T H E S I S

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by

A L E X A N D E R R. F E R G U S O N,

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T I T L E of T H E S I S.

The leucocytosis of Variola with a study of the haematopoietic organs in the disease, and also of the lesions of the Skin.

I N T R O D U C T I O N.

The material on which the whole of my observations are based was provided by the epidemic of Smallpox which prevailed in Glasgow from the latter part of 1899, to 1901.

I wish therefore to express my indebtedness to the Visiting Physician and Resident Staff of the City of Glasgow Smallpox Hospital for the many facilities offered me during my daily examinations of the patients there.

The work has been done in the University Pathological Institute, and I desire to express my warm appreciation of Professor Muir's kindness, not only in granting me facilities for its prosecution, but for valuable suggestions as to the manner in which it should be carried out.

With regard to the Illustrations, which have all been made from my own preparations, the very perfect drawings of Figs. 5 & 14, as well as the photographs in Figs. 6, 10, 11, 12, 13, 18 (upper) 24 & 26 are the work of Mr. Richard Muir. Figs. Nos. 15 & 25 are reproduced from drawings by Mr. Jas. Gilmour. The photographs in Fig. 7 were done by Dr. Thomas Reid LLD. The remaining photographs were done in the Pathological Institute, here, and the Water colour sketches are my own.

THE BLOOD IN VARIOLA.

HISTORICAL & LITERARY REVIEW.

The alteration in the physical properties of the blood during the more severe forms of Variola especially, is sufficiently striking. In the earlier stages of the disease, it more or less rapidly undergoes a change in colour, deepening in tint, until shortly before death in haemorrhagic cases, it becomes almost black in appearance. It also becomes glutinous or sticky, but rarely forms a coagulum rich in fibrine. Post-mortem, the blood in confluent or haemorrhagic cases is fluid and remains so "in vitro" for a considerably longer period than normal.

In conducting my observations on the blood, I frequently noticed that both in the tolerably severe and in the worst forms of the disease, the blood coagulated readily over the site of puncture in the earlier stages of the malady, but that about the period of acme of the eruption, little tendency towards coagulation

could be observed. Indeed, after puncture of the ear in some of the most severe cases examined fluid blood continued to ooze from the puncture in small quantities for two to three hours.

In this connection it is of interest to note that MM. Andral and Gavarret who examined the blood in five cases of confluent Smallpox in the earlier part of the last century, stated that "while the blood corpuscles differed but slightly from their healthy proportion, the quantity of fibrine varied very considerably. In no case however was the increase above the physiological proportion, when present, anything but trifling". (Reference in Dr. Camp's paper; see Appendix).

In mild cases however, during the whole period of the increase, but more particularly in the earlier stages, coagulation of the blood occurs so readily that the condition of hyperfribrinosis is naturally inferred.

The odour of the blood in Variola is also characteristic. This quality is possessed in most marked degree by the blood in haemorrhagic forms of the disease, and is usually very slight or absent in mild cases. It is not difficult to identify the heavy, sweet, and slightly nauseating character of this odour with that emitted from the subject of a confluent or

purpuric Variola during life. At a time when venesection was very regularly practised in the treatment of Variola, the odour of the blood had for some physicians (particularly, Majendie) a prognostic significance.

Generally speaking, therefore, the physical properties of the Blood in Smallpox conform to those of the more severe forms of septicaemia.

The variations in number of the red corpuscles in the blood in Variola are slight. According to Pick, moderate increase in their number may be observed about the 7th to the 9th day; more frequently, however, the differences in numbers are no greater than may be accounted for by technical errors in enumeration. In severe cases, gradual reduction in the number, amounting to from 1,000,000 to 2,000,000 per cubic millimetre has been noted. (Hayem. Arnheim.)

With regard to blood platelets, Pick states that "at the height of suppuration and for 3-4 days afterwards, these often show a noteworthy increase". Although I have not made relative enumerations of these elements, they have come under such repeated observation in studying the leucocytes, that I can readily agree with this opinion. I would say however, that the increase in platelets may be observed in mild and tolerably severe

cases for a longer period than above indicated. I have frequently noted their presence, in considerably larger numbers than usual, as late as the 17th to the 19th days of the disease. They are on the other hand, very much reduced in the more grave cases and in those terminating fatally appear altogether absent.

Prior to the publication in 1870 of M. Brouardel's paper, our knowledge both of the occurrence and degree of leucocytosis in Variola was meagre and indefinite. This author proved the existence of a leucocytosis in the pre-eruptive stage, which increased during the development of the eruption and diminished after the incidence of pustulation. Leucocytosis was said by him to be in abeyance both in the slightest and most virulent types of the disease. Verstraeten, who published his results on the same subject in 1875, found that the leucocytosis was proportional to the severity of the case, and was accordingly most marked in haemorrhagic cases. In differing from him on this point my own results are in accordance with those of more recent observers.

The results obtained by Hayem, Halla and Pée, each of whom has examined the blood qualitatively in the different types of Variola, support the view that

leucocytosis, more or less marked, makes its appearance in all forms of the disease. Of greater importance than the foregoing, both from the number of cases (42) and the systematic manner in which they were examined is the paper by R.Pick (1893). The series of cases examined by him includes those of all degrees of severity. In accordance with other authors, the figures given in his tables show a more or less marked leucocytosis in all but the mildest forms and in confluent cases accompanied by haemorrhage. In very mild cases, (Variola Modificatissima) the increase in the numbers of leucocytes is very slight, and rarely transgresses an upper normal limit.

In more severe cases (variola vera,"or suppurative Smallpox") a leucocytosis at the time of commencement of the eruption is not demonstrable. It speedily appears however during the development of the eruption, attains its acme about the 9th-11th day and then slowly wanes, or undergoes a later increase associated with the setting in of complications.

The leucocytosis recorded by Pick in confluent and haemorrhagic cases is insignificant, and its augmentation was traced by him to the occurrence of suppuration or complications.

Pustulation in Smallpox, in Pick's view, was always caused by a secondary invasion of pyogenic organisms, and it was not therefore the manifestation of an essential phase of the disease. He was thus led to the remarkable conclusion that Variola in general is not accompanied by leucocytosis. My observations on the histology of the eruption, and the contents of its elements (see next Section) have induced me to form a different opinion.

The important works on this subject by Dr. Emile Weil published in 1901, and the communications of MM Courmont and Montagard, published in the same year, are the only monographs in existence, so far as I am aware, in which the quantitative study in the variations of the different types of leucocytes has been made the subject of research.

The greater part of my work was done contemporaneously with that of Weil, and his admirable Thesis came into my hands when my own observations were practically completed.

He examined 24 cases of various forms of the disease at intervals of two or three to five or six days. One case of Confluent Smallpox was examined daily. Isolated observations on nineteen other cases are appended to his tabulated results. As the field of observation covered by Weil largely corresponds with my own, I shall have frequent occasion to allude to his work.

The latter authors, who investigated the subject during the epidemic at Lyons in 1899, examined in all twenty-nine cases, the examination of these being for the most part performed daily and in some cases twice daily.

The conclusions of M.Weil and of MM. Courmont and Montagard, which differ only in matters of detail may be briefly summarised as follows:-

(1) Variola is always accompanied by a leucocytosis characterised by a notable increase in the mononuclear cells of small and medium size.

(2) During the stage of vesiculation, pustulation and dessication of the eruption alike, the polymorphonuclear leucocytes are proportionately reduced in numbers.

(3) This special leucocytosis is accompanied, rarely in slight cases, but regularly in graver cases, by the appearance in the blood of cellular types not normally found there viz:-

(a) Intermediate or transitional forms of the neutrophile cells.

(b) Mononuclear neutrophiles (Myelocytes).

(c) Nucleated red blood corpuscles.

(d) Mononuclear Eosinophiles.

(e) Very large (giant forms) of nongranular mononuclear cells.

(f) Plasma Cells. (Weil).

(4) In haemorrhagic cases, a leucocytosis if present at all, only attains feeble proportions.

(5) Cases terminating fatally are characterised by a more or less ubrupt fall in the number of leucocytes.

MM. Courmont and Montagard have further specially investigated the blood of infants and children (from 19 days old to 8 years of age) the subjects of Smallpox. The results of these observations which have not yet been published in full, show that the general characters of the leucocytosis in the child are the same as in the adult. Amongst the differences noted, the more frequent appearance of nucleated red corpuscles in the infant is one which, a priori might have been anticipated.

My results are in agreement in all important respects with those of the French authors just mentioned. Any differences which exist will be best treated as they

occur in the various parts of my work, and I shall therefore proceed to record the results of my observations on the blood.

Before doing so, however, it is necessary to indicate the precise significance which I have attached to the terms by which the different types of leucocytes are designated.

POLYMORPHO-NUCLEAR NEUTROPHILE.

Besides the common type of leucocyte so designated, I have included under this name, neutrophile cells (occasionally with scanty granulations) whose nuclei were comparatively simple in form, showing little lobulation. These (see Fig. 1 .) which constitute 3% to 5% of the total number of leucocytes in mild cases, and a somewhat larger proportion in grave cases, correspond with the "Formes de transition neutrophiles" of the French authors.

I have also reckoned as cells belonging to this class the results of degeneration or fragmentation of undoubted polymorpho-nuclear leucocytes.

Weil has applied the misleading and quite unnecessary name of "small pseudo-lymphocyte neutrophile" to such a product, attributed by Ehrlich to the result of fragmentation of a polymorpho-nuclear cell. This

process of polymorpho-nuclear destruction in the blood of severe cases of Variola is however, not so exceptional as Weil regards it. (See Fig. 4).

(2) LYMPHOCYTE. (Small Mononuclear).

The numerous gradations in size presented by the hyaline cells of both classes in Variola have caused the inclusion under this category not only of cells whose characters conform to the classical description of the lymphocyte, but also of mononuclear cells of somewhat larger size than the latter, with a nucleus staining much less deeply than that of the ordinary lymphocyte. Although this arrangement is doubtless arbitrary it appeared to me preferable to that adopted by Weil, who separates these types, designating the former the "lymphocyte" and the latter, the "mononucleaire moyen".

(3) LARGE HYALINE CELL. (Large Mononuclear).

This class includes not only the large cells with relatively abundant protoplasm and oval, usually excentrically placed and feebly staining nuclei, but also the rarer examples of the following non-granular cells:-

"Irritation" forms. (Turck). These are mononuclear cells whose protoplasm assumes a chocolate brown tint when stained by Ehrlich's triacid fluid, and whose nucleus, generally excentrically placed, is devoid of

chromatin filaments. The majority of these cells are of about the same dimensions as the large mononuclear cell above described.

As Turck points out, they make their appearance in the blood under the same conditions as the Myelocyte, and they are believed by him to originate in the bone marrow.

Plasma cells. These, which, it is believed, are derived from the fixed cells of connective tissues, and are met with especially in such tissues undergoing pathological proliferative changes, are thus described by Weil, who claims to have been the first to have recorded their presence in the blood. They are oval cells of large size, with relatively large rounded or oval nucleus. The latter is composed of "several chromatic filaments which converge towards the centre, without uniting there, so that the less deep parts of the nucleus cause a radiate appearance like the spokes of a wheel". The homogeneous protoplasm stains deeply with thionine, more faintly with acid dyes. The very exceptional examples of these cells which I have encountered, have been placed in this category.

(4) EOSINOPHILES.

This category includes in my statements, not only the

polymorpho-nuclear but also the mononuclear cells of the class. The latter however occur but rarely in the blood and their presence will be mentioned in the summary of notes made during observation of the blood appended to the tables dealing with each case.

(5) NUCLEATED RED CORPUSCLES.

Although the smaller form of nucleated red corpuscle (normoblast) is that which most frequently occurs in the blood of severe forms of Smallpox, the larger forms (megaloblasts) also occur in small numbers. (The occurrence of the latter will be mentioned in the notes attached to the particular cases).

(6) MYELOCYTES.

This class includes only the mononuclear neutrophile cells as described by Ehrlich.

METHODS & GENERAL TECHNIQUE EMPLOYED.

Almost without exception the lower lobe of the ear was chosen as the site of puncture for obtaining blood. The ear was first washed with 1-40 Carbolic acid solution, and afterwards with Methylated Spirit. In cases where the lobe of the ear was comparatively free from crusts, or evidences of eruption, the Carbolic lotion was not used. In most of the milder cases examined, the same Ear was punctured daily, and in none of the cases was any trouble caused by successive punctures. Care was always taken that the actual site of puncture was free from eruptive manifestations, and in order to insure this, it was sometimes necessary to choose another site, either the opposite ear or the finger being taken.

For the counting of leucocytes in the fresh blood, the "leucocyte pipette" and ruled slide of the Thoma-Zeiss apparatus was used exclusively. The solution used for the dilution of the blood in the pipette was a 3% aqueous solution of Acetic acid which was tinted by the addition of one or two drops of a concentrated watery solution of Methyl green (as used in the preparation of Ehrlich's Triacid fluid).

All the leucocytes contained within the area

covered by the ruled lines on the slide intersecting at right angles were counted. The capacity of the cell covered by this area is 1/10 cubic m.m. and, as the blood is diluted with 10 vols. of solution in the pipette, the number of leucocytes in 1 cubic millimetre of undiluted blood is obtained by multiplying the number counted in the manner detailed above by 100.

In every case, the numbers given in the accompanyong tables represent the mean result of 2 or 3 counts When these differed from one another, or the result from those of the previous days, the result was rejected, a fresh enumeration being made after re-filling the pipette The whole of the nucleated cells encountered in the fresh blood were counted.

Film-preparations of the blood were always made at the same time and, in most of the cases, such preparations were also made from the contents of the vesicles or pustules at intervals of a few days.

A good many of the dried blood film preparations were, in the earlier stage of the investigation, fixed in a mixture of Formaline and Absolute Alcohol, (Formaline 40% Formic Aldehyde 10 c.c. Absolute Alcohol 90 c.c.) and stained in one or other of the following ways.

(a) Mayer's Haemalum and Eosin.

(b) Eosine (equal parts of a 1% alcoholic sol. and water) and Methylene blue.

(c) Eosine and Carbol-thionin blue.

The necessity, however, of having specimens in which the granules of the leucocytes as well as those of the associated cells of the bone marrow, if present, were characteristically stained, became so quickly apparent that I adopted the practice of fixing all blood films by dry heat and staining them by Ehrlich's Triacid fluid. All the differential estimations of the leucocytes given in the following Tables are based on films treated in this manner. A temperature of 110° C maintained for 1-1½ hours was found to yield uniformly good results.

The differential estimations, for the first two or three days of observation, are based in each case on 500 leucocytes of all varieties counted. Thereafter, when the character of the changes occurring in the white cells was becoming manifest, 300 leucocytes were counted as a basis for the percentage calculation, and, although in a few instances, the proportions per cent were calculated on 200 leucocytes counted, it may be stated generally that 300 forms the basis on which the numbers in the Tables are given. It must be added that the whole

series of leucocyte-counts in the fresh blood was made at the same time daily viz. 9 to 11 pm.

CLASSIFICATION of CASES.

I have systematically examined in this manner sixteen cases of Variola. These I have arranged in three groups, according to the severity of the disease thus:-

GROUP 1. 8 CASES.

Mild cases characterised by discrete eruption in which the malady, occurring in previously vaccinated subjects, fulfilled a normal course.

GROUP 2. 3 CASES.

Grave cases, terminating favourably, ushered in by severe prodromata, and accompanied by an abundant eruption, semi-confluent generally on the face, and showing the same tendency in certain areas over the trunk or limbs.

GROUP 3. 5 CASES.

The most severe class of cases, including confluent and haemorrhagic types of the disease. With one exception

(severe attack in unvaccinated sunject) all the cases in this group terminated fatally.

In the following statement of my results, two sets of tables accompany each case. In the first, the proportions per cent of the various types of leucocytes with their total number per cubic millimetre are given for each day of examination. In the second, the absolute numbers of the various types of leucocytes calculated from their per centage numbers, are stated. The results given in the latter tables have further been graphically represented by a series of charts inserted in connection with each case.

A summary of notes made during the daily examinations of the blood, recording the changes presented in the various cellular types, as well as the presence of unusual forms, is appended to the tables in each case.

For purposes of reference, the cases are numbered consecutively.

GROUP 1.

CASE No.1. JOHN M. aet. 26. Illness commenced with usual initial signs. Eruption discrete and rather plentiful on face and scalp; somewhat sparse on trunk and limbs. Eruptive elements exhibit some variations in size, and are as a whole smaller than usual.

JULY 7th. Commencing dessication of eruption on the face; fully pustular elsewhere.

JULY 10th. Crusting and dessication general. Very few small pustules remain on legs and dorsa of feet.

JULY 14th. Eruption rapidly disappearing. Small abscess on left thigh noted.

JULY 21st. General condition good. Slough has separated from abscess in thigh. Remains of eruption visible as stained patches.

JULY 26th. Patient well, but for some time continued to develop successive crops of deep boils, with contained sloughs.

CASE No.1. JOHN M. continued.

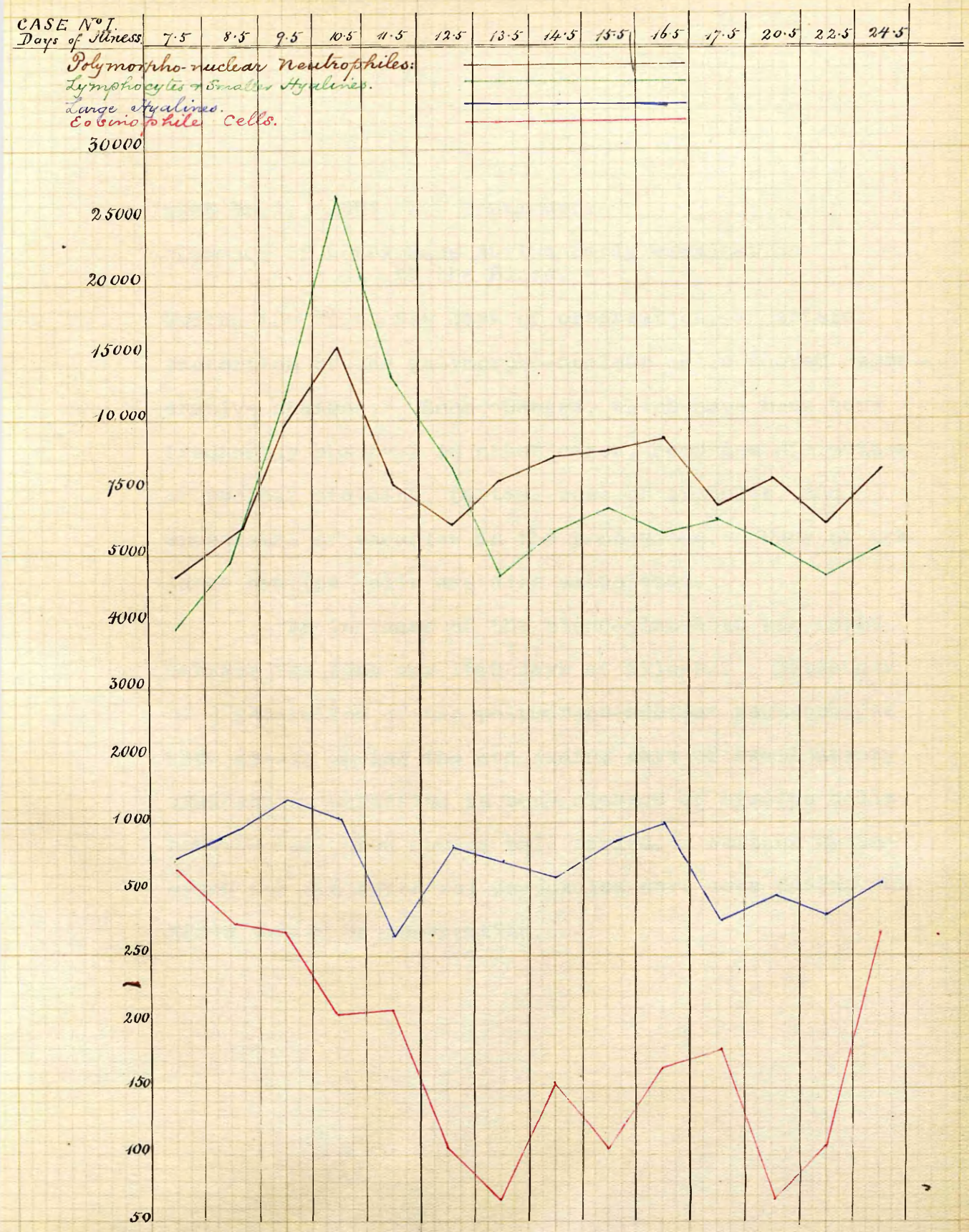
July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.
2.	5.5.	6566.				
3.	6.5.	9150.				
4.	7.5.	9850.	47.0.	39.0.	7.5.	6.5.
5.	8.5.	11,966.	48.0.	41.0.	8.0.	3.0.
6.	9.5.	23,100.	41.5.	51.5.	5.5.	1.5.
7.	10.5.	41,866.	36.5.	60.5.	2.5.	.5.
8.	11.5.	21,366.	36.0.	61.5.	1.5.	1.0.
9.	12.5.	15,600.	38.7.	55.3.	5.3.	.7.
10.	13.5.	13,466.	58.5.	35.0.	6.0.	.5.
11.	14.5.	15,260.	58.0.	34.5.	6.5.	1.0.
12.	15.5.	16,550.	54.0.	40.0.	5.3.	.7.
13.	16.5.	16,633.	57.0.	36.0.	6.0.	1.0.
14.	17.5.	13,733.	50.0.	46.0.	2.7.	1.3.
15.	18.5.	14,600.				
17.	20.5.	13,833.	57.0.	39.0.	3.5.	.5.
19.	22.5.	11,500.	54.5.	41.0.	3.5.	1.0.
21.	24.5.	14,433.	56.7.	37.3.	3.7.	2.3.
24.	27.5.	10,733.				

CASE No.1. JOHN M---.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Total.
4.	4629.	3841.	738.	642.	9850.
5.	5743.	4906.	957.	360.	11,966.
6.	9586.	11896.	1270.	348.	23,100.
7.	15281.	25329.	1046.	210.	41,866.
8.	7691.	13140.	320.	215.	21,366.
9.	6037.	8627.	827.	109.	15,600.
10.	7877.	4713.	807.	69.	13,466.
11.	8545.	5951.	610.	154.	15,260.
12.	8937.	6620.	877.	116.	16,550.
13.	9480.	5988.	998.	167.	16,633.
14.	6860.	6317.	370.	180.	13,733.
17.	7885.	5395.	484.	69.	13,833.
19.	6267.	4715.	402.	116.	11,500.
21.	8183.	5383.	534.	333.	14,433.

CASE N°I


Days of Illness
7·5
8·5
9·5
10·5
11·5
12·5
13·5
14·5
15·5
16·5
17·5
20·5
22·5
24·5
Polymorpho-nuclear Neutrophiles:
Lymphocytes & Smaller Hyalines.
Large Hyalines.
Eosinophile Cells.
30000
25000
20000
15000
10000
7500
5000
4000
3000
2000
1000
500
250
200
150
100
50

CASE No.1. JOHN M. continued.

Summary of notes made during daily examination of the Blood.

During the first few days of observation, a certain proportion of the polymorpho-nuclear cells showed degenerative changes. Such changes, which have been very frequently observed in other cases, comprise diminution of nuclear staining, partial loss of granules, and appearance of vacuoles in the protoplasm. Many of the large hyaline cells are also vacuolated.

An increase of the blood-platelets was noted between the 10th and 15th days of illness. Evidences of degeneration of the polymorpho-nuclear neutrophiles were absent during the concluding days of examination; vacuolation occurring in both classes of hyaline cells however was noted during this period. Neither Myelocytes nor nucleated red corpuscles were seen during the whole period of observation.

CASE No.2. MARY W. aet. 36. Patient became ill on June 29th. When she first came under observation (5th. day of illness) a small but abundant vacuolar eruption was present on the Face. The eruption was also plentiful but discrete over trunk and limbs.

JULY 8th. Dessication and crusting of eruption appeared on face. Over the body and limbs, the eruption is still fully pustular.

JULY 11th. Commencing crusting of eruption visible in most of the elements over trunk and limbs.

JULY 14th. Majority of crusts have desquamated, leaving purplish stained patches.

Subsequently, a slow but uneventful convalescence.

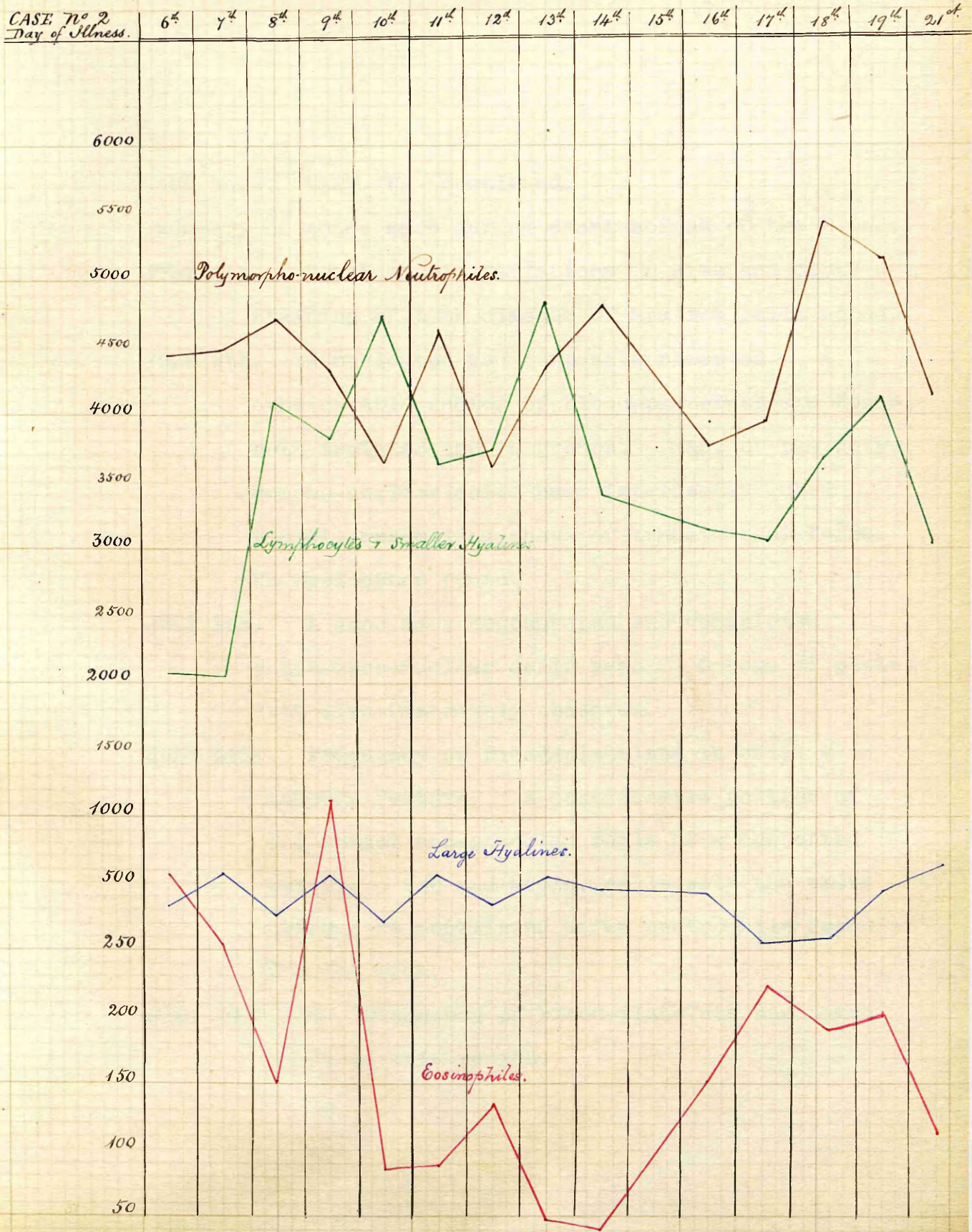
CASE No.2. MARY W. continued.

July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.
3.	5th.	7200.				
4.	6th.	7430.	59.5.	27.5.	5.5.	7.5.
5.	7th.	7366.	66.0.	27.5.	8.0.	3.5.
6.	8th.	9366.	50.7.	43.7.	4.0.	1.6.
7.	9th.	9800.	44.0.	39.0.	5.5.	11.5.
8.	10th.	8800.	41.5.	54.0.	3.5.	1.0.
9.	11th.	8950.	52.0.	40.5.	6.5.	1.0.
10.	12th.	7966.	45.3.	47.0.	6.0.	1.7.
11.	13th.	9800.	44.5.	49.5.	5.5.	.5.
12.	14th.	8750.	55.0.	39.0.	5.5.	.5.
13.	15th.	9750.				
14.	16th.	7466.	50.5.	42.0.	5.5.	2.0.
15.	17th.	7466.	53.0.	40.5.	3.5.	3.0.
16.	18th.	9600.	56.5.	38.5.	3.0.	2.0.
17.	19th.	9966.	52.0.	41.5.	4.5.	2.0.
19.	21st.	7933.	52.3.	38.0.	8.3.	1.4.

CASE No.2. MARY W. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Fosino-philes.	Total.
4.	4421.	2043.	408.	558.	7430.
5.	4493.	2025.	589.	259.	7366.
6.	4748.	4093.	374.	151.	9366.
7.	4312.	3822.	539.	1127.	9800.
8.	3652.	4752.	308.	88.	8800.
9.	4654.	3625.	582.	89.	8950.
10.	3608.	3744.	478.	136.	7966.
11.	4361.	4851.	539.	49.	9800.
12.	4812.	3412.	481.	45.	8750.
13.					
14.	3770.	3135.	410.	151.	7466.
15.	3957.	3023.	261.	225.	7466.
16.	5424.	3696.	288.	192.	9600.
17.	5182.	4136.	448.	200.	9966.
19.	4149.	3014.	658.	112.	7933.


CASE. No 2
Day of Illness.
6th
7th
8th
9th
10th
11th
12th
13th
14th
15th
16th
17th
18th
19th
21st
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
250
200
150
100
50
Polymorpho-nuclear Neutrophiles.
Lymphocytes + Smaller Hyalines.
Large Hyalines.
Eosinophiles.

CASE No.2. MARY W. continued.

Summary of notes made during examinations of the Blood.

JULY 4th. Considerable variations in size and depth of staining of both classes of hyaline cells noted.

JULY 8th. A nucleated red corpuscle observed. A considerable number of blood-platelets are found, both isolated and in groups. Manu of the polymorpho-nuclear cells have imperfectly lobed nuclei, resembling those of transitional forms. No Myelocytes found.

JULY 9th. A good many degenerated and vacuolated polymorpho-nuclear cells seen. Groups of platelets also frequently observed.

JULY 10th. Frequency of blood-platelets is still a notable feature. A considerable portion of the larger non-granular cells have contorted nuclei. Now and again, cells with the above characters containing a few neutrophile granules are met with.

JULY 14th-16th. Frequency of blood-platelets was noted still at this period.

CASE No.3. JAMES Mc F. aet. 25.

Illness commenced on July 5th. When first observed (July 8th.) patient presented a moderately abundant eruption on the face, with a scanty distribution of small papules over trunk and limbs.

JULY 10th. Commencing pustulation of facial eruption. A few vesicles present over body but the majority of elements are still papular.

JULY 11th. Pustulation more general.

JULY 14th. Facial eruption has dessicated without much crusting. Eruption over body slightly crusted. A few pretty fully pustular elements still present on lower limbs.

JULY 19th. Eruption has receded more quickly than usual. Convalescence without complications.

CASE No.3. JAMES Mc F.

July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.
8.	4th.	7133.	69.0.	26.5.	4.0.	.5.
9.	5th.	6400.				
10.	6th.	14,533.	58.0.	32.5.	5.5.	4.0.
11.	7th.	7350.	60.0.	35.5.	3.0.	1.5.
12.	8th.	8666.				
13.	9th.	9100.	47.0.	47.0.	4.0.	2.0.
14.	10th.	8500.	56.5.	39.5.	1.5.	2.5.
15.	11th.	7133.	47.0.	45.5.	4.0.	3.5.
16.	12th.	6540.	51.3.	44.0.	2.7.	2.0.
17.	13th.	7200.	53.0.	40.7.	5.6.	.7.
18.	14th.	6533.	53.0.	39.5.	6.0.	1.5.
19.	15th.	6400.	59.5.	30.0.	7.5.	3.0.
21.	17th.	7000.				

CASE No.3. JAMES Mc F. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

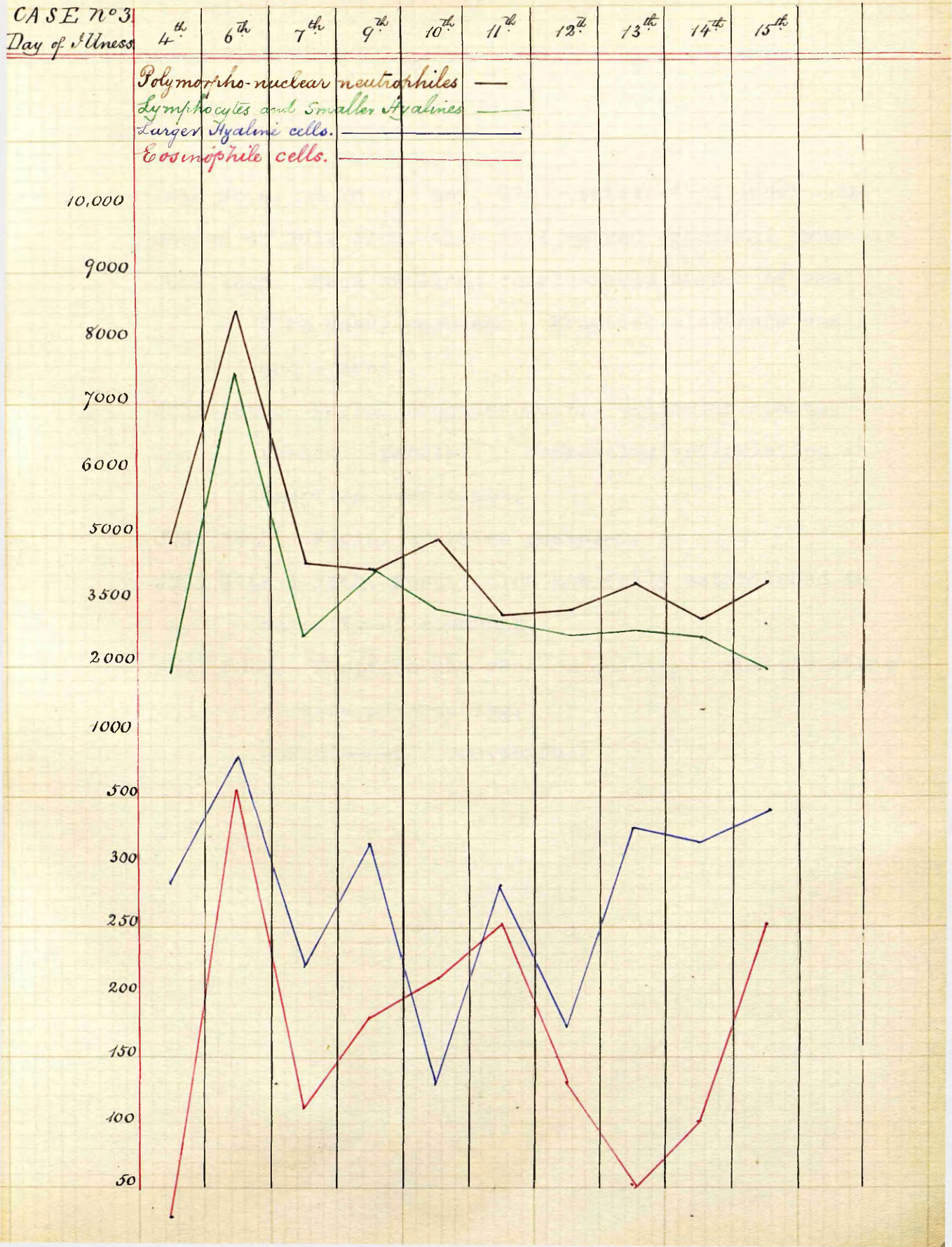
July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Total.
8.	4922.	1890.	285.	36.	7133.
10.	8429.	7423.	799.	582.	14,533.
11.	4410.	2609.	220.	111.	7350.
13.	4277.	4277.	364.	182.	9100.
14.	4802.	3357.	128.	213.	8500.
15.	3352.	3245.	285.	251.	7133.
16.	3355.	2878.	176.	131.	6540.
17.	3816.	2930.	403.	51.	7200.
18.	3462.	2580.	391.	100.	6533.
19.	3808.	1920.	480.	192.	6400.

Summary of notes made during examinations of Blood.

JULY 8th. At this comparatively early stage in a mild case, many of the polymorpho-nuclear cells show degenerative changes. Many of the smaller hyaline cells are also vacuolated. One nucleated red corpuscle found in counting 300 leucocytes.

During subsequent days of examination (10th, 12th, and 13th days of illness) either one or two myelocytes were met with in counting 300 leucocytes.

CASE N°3


Day of Illness
4th
6th
7th
9th
10th
11th
12th
13th
14th
15th
Polymorpho-nuclear neutrophiles
Lymphocytes and Smaller Hyalines
Larger Hyaline cells.
Eosinophile cells.
10,000
9000
8000
7000
6000
5000
3500
2000
1000
500
300
250
200
150
100
50

CASE No.4. M Mc C. aet. 27. Patient's illness commenced on July 11th. with well marked prodromal symptoms

JULY 13th. Face swollen: considerable number of small firm dusky papules. Eruption elsewhere small and sparse.

JULY 15th. Facial eruption partly vesicular, partly vesiculo-papular. Commencing vesiculation in eruption over limbs.

JULY 16th. Facial eruption pustular.

JULY 17th & 18th. Pustulation now fully established in majority of elements.

JULY 20th. Eruption has receded quickly. Little signs of general crusting.

Convalescence uneventful.

CASE No.4. M Mc C. continued.

July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.
13.	3rd.	5433.				
14.	4th.	4933.	50.7.	37.0.	5.3.	7.0.
15.	5th.	6425.				
16.	6th.	8533.	54.8.	35.2.	5.7.	4.3.
17.	7th.	11,350.	56.3.	35.3.	4.3.	4.0.
18.	8th.	17,366.	58.0.	35.3.	3.3.	3.3.
19.	9th.	20,200.	45.0.	51.0.	1.5.	2.5.
20.	10th.	15,800.	46.4.	47.6.	3.6.	2.3.
21.	11th.	19,200.	57.0.	40.3.	2.0.	.7.
22.	12th.	18,266.				
23.	13th.	15,100.	64.0.	31.7.	4.0.	.3.
24.	14th.	13,500.	55.0.	41.5.	3.0.	.5.
25.	15th.	15,966.	65.0.	31.0.	1.7.	2.3.
26.	16th.	12,625.	63.0.	32.7.	3.0.	1.3.
27.	17th.	13,300.				
31.	21st.	8,700.				

CASE No.4. M Mc C. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Total.
14.	2501.	1825.	261.	346.	4933.
15.					
16.	4678.	3003.	486.	366.	8533.
17.	6390.	4006.	488.	466.	11,350.
18.	10,072.	6130.	573.	591.	17,366.
19.	9090.	10,302.	303.	505.	20,200.
20.	7331.	7521.	569.	379.	15,800.
21.	10,944.	7737.	384.	135.	19,200.
23.	9664.	4787.	604.	45.	15,100.
25.	10,378.	4949.	271.	368.	15,966.
26.	7953.	4128.	379.	165.	12,625.

Summary of notes made during examinations of Blood.

JULY 14th. Many of the polymorpho-nuclear cells exhibit defective nuclear staining and only partial granule-staining. Some of these as well as the lymphocytes show vacuolation.

JULY 17th. A nucleated red corpuscle seen to-day. Some of the Eosinophile cells in addition to the varieties noted yesterday, show vacuolation.

JULY 18th. Many polymorphs are of "transitional type".

CASE. Nº 4.
Day of Illness.

JULY 19th. One Myelocyte seen to-day.

JULY 23rd-26th. Degenerative changes still present in polymorpho-nuclear cells and lymphocytes. Frequency of small collections of blood-platelets noted on these days.

CASE No.5. JAMES G. aet. 26.

JULY 18th. Patient first came under observation on 7th day of illness. Face very oedematous and covered with abundant Variolar eruption in almost fully pustular stage. Here and there patches of closely set elements have coalesced. The eruption, though abundant on face and limbs is discrete. A few shallow ulcers on tongue and buccal mucous membrane from rupture of vesicles. Fauces show moderately abundant eruption with marked catarrhal symptoms.

JULY 19th. Eruption on face fully pustular. Crust-formation commencing.

JULY 2oth. Eruption on trunk and limbs fully pustular. The elements are large, dense and prominent. Their contents show a few red corpuscles. Patient throughout expressed little sense of illness beyond the discomfort associated with the eruption.

JULY 21st. Crusts on face have the appearance of large placques, and are splitting in various directions. Eruption elsewhere still dense; very thin puriform contents with some blood.

JULY 23rd. Eruption dessicating rapidly on face and neck. Pustules on backs of hands and arms have begun to collapse prior to crusting; elsewhere, eruption consists of prominent turbid vesicles.

JULY 26th. Eruption slowly receding.

AUG.1st. Face shows traces of crusts with irregular macular staining. Eruption generally has undergone dessication; patient practically convalescent from Smallpox.

CASE No.5. JAMES G. continued.

July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.	Myelo-cytes %.
18.	7th.	16466.	80.0.	15.2.	2.6.	1.71.	.57.
19.	8th.	14,533.	71.1.	19.6.	3.1.	5.7.	.5.
20.	9th.	15,250.	46.0.	35.5.	12.5.	6.0.	
21.	10th.	15,433.	44.0.	43.5.	6.5.	6.0.	
22.	11th.	17,566.	45.5.	41.2.	9.4.	3.9.	
23.	12th.	14.766.	51.0.	42.5.	5.5.	1.0.	
24.	13th.	12,433.	57.4.	38.3.	1.3.	3.0.	
25.	14th.	12,800.	62.7.	33.3.	1.7.	2.3.	
26.	15th.	10,950.	51.8.	40.8.	2.45.	4.0.	.93.
27.	16th.	10,000.	54.3.	34.6.	5.0.	3.0.	3.0.
28.	17th.	11,933.	60.4.	35.6.	.8.	2.4.	.8.
29.	18th.	11,366.	48.2.	47.3.	2.4.	2.1.	
30.	19th.	10,900.	60.3.	35.3.	1.0.	3.4.	
31.	20th.	10,450.	60.3.	33.7.	3.7.	2.3.	
Aug. 2.	22nd.	10,533.					
4.	24th.	9,950.					

CASE No.5. JAMES G. continued.

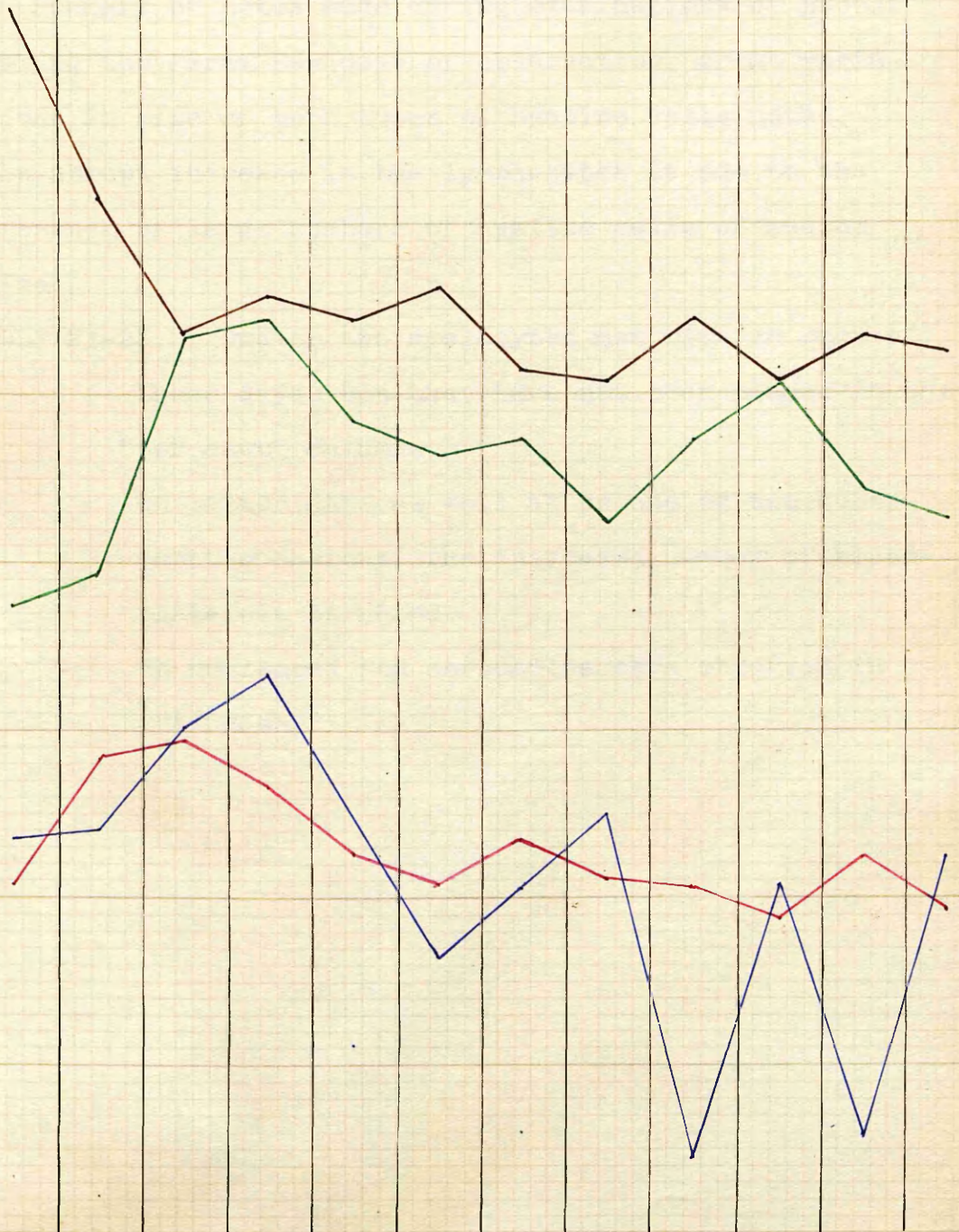
ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Myelo-cytes.	Total.
18.	13,173.	2503.	428.	280.	82.	16,466.
19.	10,333.	2848.	450.	828.	74.	14,533.
20.						
21.	6790.	6713.	1003.	927.		15,433.
22.	7992.	7237.	1651.	686.		17,566.
24.	7136.	4762.	161.	374.		12,433.
25.	8025.	4262.	218.	295.		12,800.
26.	5672.	4467.	263.	438.	110.	10,950.
27.	5430.	3460.	500.	300.	310.	10,000.
28.	7207.	4248.	95.	286.	97.	11,933.
29.	5478.	5376.	273.	239.		11,366.
30.	6573.	3848.	109.	370.		10,900.
31.	6301.	3521.	386.	242.		10,450.

CASE. No 5.

Day of Illness.	7th	8th	10th	11th	13th	14th	15th	16th	17th	18th	19th	20th

15,000
12,500
10,000
7500
5000
4000
3000
2000
1000
500
250
200
150
100
50



CASE No.5. JAMES G. continued.

Summary of notes made during examinations of Blood. During the first few days of observation, great variations in size of both types of hyaline cells noted. The abrupt increase in the lymphocytes is due to the presence of large numbers of hyaline cells of medium size.

JULY 21-23. One or two myelocytes met with on each of these days, but they have not been placed in the "per cent" columns.

On latter date as well as on one or two subsequent occasions, the increased number of blood-platelets is noted.

No nucleated red corpuscles were observed in this case.

CASE No.6. Mrs. S. aet.35.

This was probably the mildest case examined. Patient had no sense of illness after the prodromal stage had passed off.

The eruption, which commenced on the night of the 24th-25th July, was composed of about twenty papules on the face, with a very scanty papular eruption on the trunk and limbs.

The elements of the eruption became during the next few days more prominent, and by July 29th. pustulation was most pronounced on the face, though this scarcely occurred at all in that present on the limbs. Convalescence proceeded without any unusual feature.

CASE No.6. Mrs. S. continued.

July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.
25.	5th.	3275.	57.7.	31.3.	7.3.	3.7.
26.	6th.	3500.	52.0.	36.5.	6.5.	5.0.
27.	7th.	3750.	66.3.	20.7.	8.3.	4.7.
28.	8th.	5275.	66.0.	23.3.	4.3.	6.3.
29.	9th.	7475.	61.0.	27.0.	6.0.	6.0.
30.	10th.	7150.	56.7.	31.0.	3.7.	8.6.
31.	11th.	5200.				
Aug.						
1.	12th.	6200.	40.5.	49.0.	8.0.	2.5.
2.	13th.	5996.				
3.	14th.	5500.	42.5.	48.0.	6.5.	3.0.
4.	15th.	7350.				
5.	16th.	6400.				

CASE No.6. Mrs S. continued.

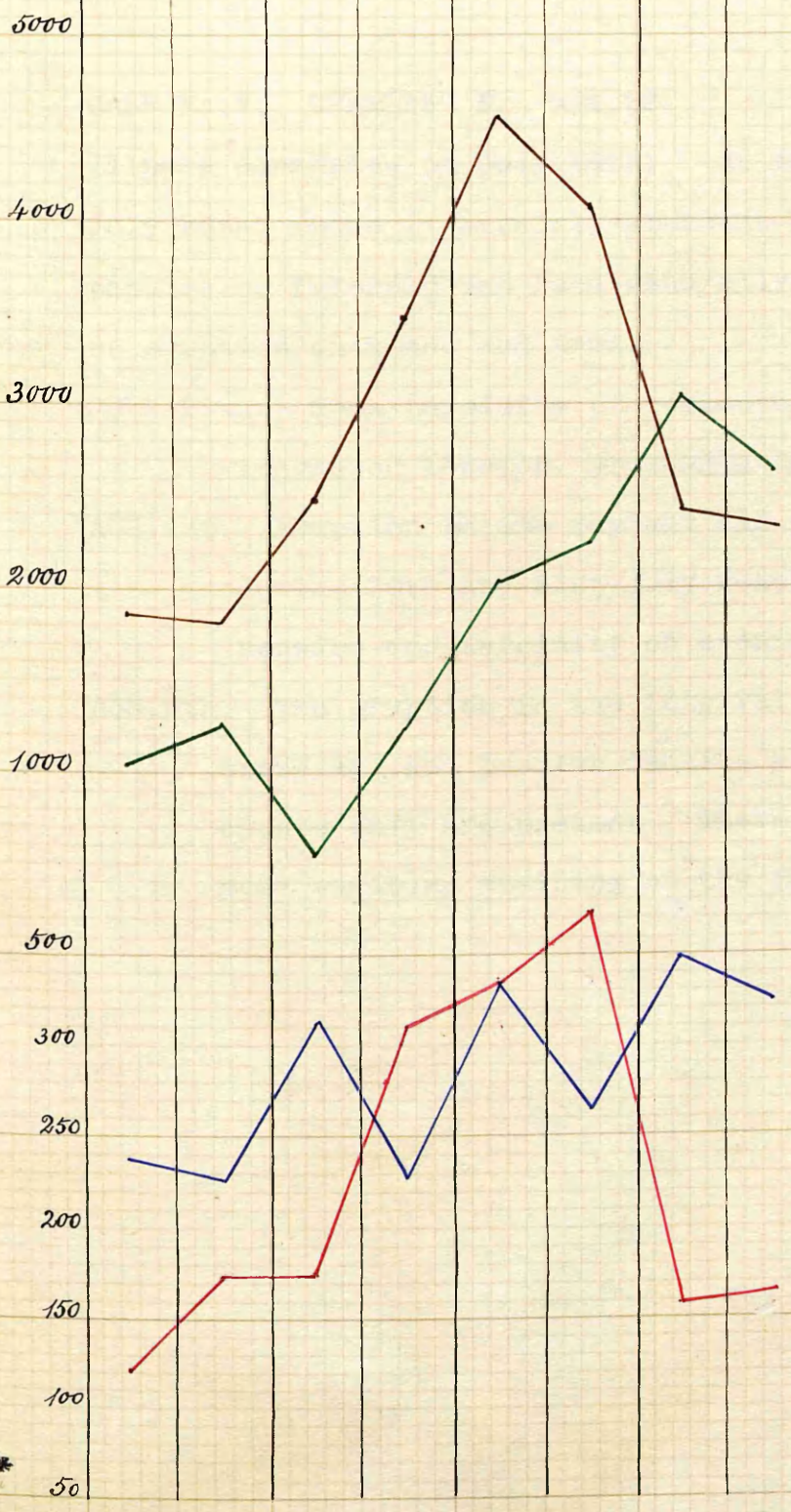
ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Total.
25.	1889	1025.	239.	122.	3275.
26.	1820.	1277.	227.	176.	3500.
27.	2486.	776.	311.	177.	3750.
28.	3481.	1229.	227.	338.	5275.
29.	4560.	2018.	448.	449.	7475.
30.	4054.	2216.	264.	616.	7150.
Aug.					
1.	2411.	3038.	496.	155.	6200.
3.	2337.	2640.	357.	166.	5500.

Summary of notes made during examinations of Blood. During the first few days of observation, many of the smaller hyaline cells showed degenerative changes, often associated with vacuolation. Polymorpho-nuclear cells well formed, but showing considerable variations in size. Numerous small masses of blood-platelets observed. From July 29th till close of observations, degenerative changes were observed in a certain proportion of polymorpho-nuclear cells; a small proportion of the larger hyaline cells were noted as possessing contorted bu not deeply lobulated nuclei. Neither myelocytes nor nucleated red corpuscles were observed at any period.

CASE N° 6.

Day of Illness.	5th.	6th.	7th.	8th.	9th.	10th.	12th.	14th.



CASE No.7. CHARLES F. aet.32.

Illness commenced on July 24th. At date of observation July 28th. there is a fairly abundant crop of vesico-papules on Forehead and Face generally; a moderate amount of eruption on hands and arms.

JULY 29th. Some turbidity of comtents of vesicles with increased tension, producing discomfort.

AUG.1st. Eruption became rapidly and generally pustular during 30th and 31st July reaching the acme of tension and turbidity on evening of latter date.

AUG.5th. The eruption in the interval has receded steadily, and papular remains with occasional crusts only are present. There is a good deal of post variolar staining on the face and limbs,

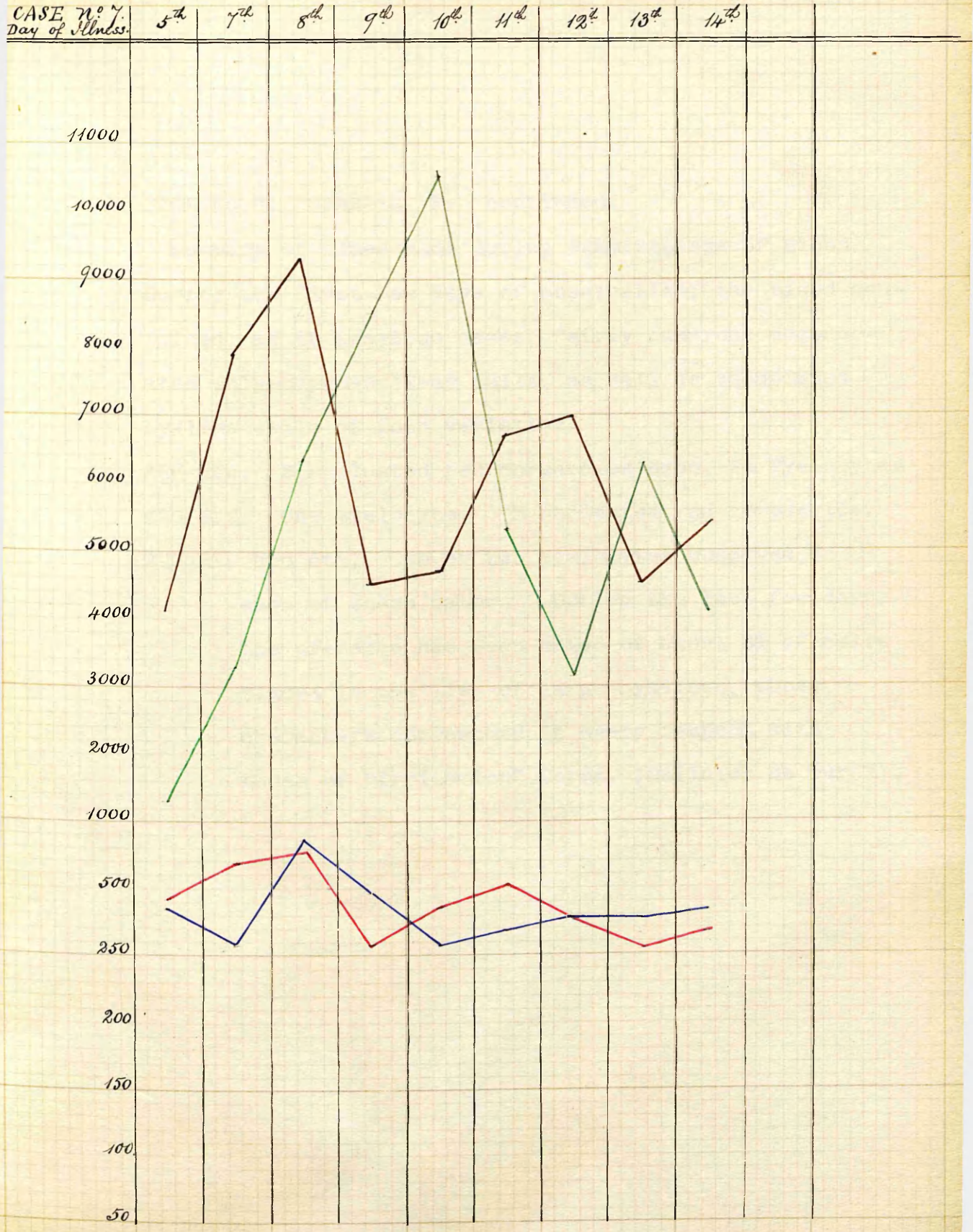
CASE No.7. CHARLES F. continued.

July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.
28.	5th.	6325.	65.0.	21.0.	7.0.	7.0.
29.	6th.	8800.				
30.	7th.	11,950.	65.7.	27.0.	2.3.	5.0.
31.	8th.	16,850.	55.0.	37.3.	4.0.	3.7.
Aug.						
1.	9th.	13,750.	33.0.	61.5.	3.5.	2.0.
2.	10th.	15,900.	29.3.	66.3.	1.7.	2.7.
3.	11th.	12,850.	52.0.	41.3.	2.7.	4.0.
4.	12th.	10,800.	64.5.	29.5.	3.5.	2.5.
5.	13th.	11,425.	39.7.	54.7.	3.3.	2.3.
6.	14th.	10,240.	52.7.	40.0.	4.0.	3.3.

CASE No.7. CHARLES F. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Total.
28.	4111.	1328.	433.	453.	6325.
29.					
30.	7851.	3226.	275.	598.	11,950.
31.	9267.	6285.	674.	624.	16,850.
Aug.					
1.	4537.	8456.	481.	276.	13,750.
2.	4659.	10,542.	270.	429.	15,900.
3.	6682.	5307.	347.	514.	12,850.
4.	6966.	3078.	378.	378.	10,800.
5.	4536.	6249.	377.	263.	11,425.
6.	5396.	4096.	409.	339.	10,240.


CASE No. 7.
Day of Illness.
5th
7th
8th
9th
10th
11th
12th
13th
14th
11000
10,000
9000
8000
7000
6000
5000
4000
3000
2000
1000
500
250
200
150
100
50

CASE No.7. CHARLES F. continued.

Summary of notes made during examinations of Blood. During the first few days of observation, the blood contained, as in previous cases, fairly numerous degenerated polymorpho-nuclear cells, as well as vacuolated hyaline cells of both varieties.

AUG 2nd. 2 nucleated red corpuscles seen. No Myelocytes

AUG 3rd. One Myelocyte. 3 nucleated red corpuscles.

AUG 5th and 6th. One or two myelocytes observed on each of these dates. During the last few days, the presence has been noted of about 8% of cells placed in the list of large hyalines, whose characters correspond in every respect with these of "irritation" forms. (Cellules de Turck).

CASE No.8. JAMES C. aet. 24.

The prodromata and early evidences of eruption in this case promised a tolerably severe attack, but it afterwards pursued a mild course.

When admitted on 17th Sept. the eruption was already very plentiful on the face; the elements are here closely set and some degree of coalescence has occurred. On the forehead, the eruption assumes the form of hard, inflamed papules, while vesiculation is apparent on part of the face and neck. Abundant eruption on backs of hands and forearms. On the lower limbs, there are besides the remains of the prodromal rash, a crop of papules which are as yet, better felt than seen.

SEPT 21-22. The acme of pustulation was reached between these dates, after which the eruption receded in the usual fashion, crusting being a marked feature.

During convalescence, numerous small abscesses appeared, which were slow in healing.

CASE No.8. JAMES C. continued.

Sept.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear. %	Lympho-cytes. %	Large Hya-lines. %	Eosino-philes. %	Myelo-cytes. §	Nucleated Red Corpuscles. §
19.	7th.	11,000.	76.3.	11.0.	2.7.	10.0.	4.	8.
20.	8th.	18,100.	59.0.	31.7.	4.3.	5.0.		2.
21.	9th.	17,450.	60.0.	32.3.	4.7.	3.0.	1.	2.
22.	10th.	13,400.	59.7.	29.7.	4.0.	6.6.	2.	1.
23.	11th.	11,550.	50.7.	42.7.	4.6.	2.0.	2.	1.
24.	12th.	11,700.	47.0.	45.0.	6.0.	2.0.	2.	3.
26.	14th.	12,050.	58.0.	36.7.	4.7.	1.3.	1.	
28.	16th.	10,500.	52.0.	43.0.	2.3.	2.7.		
Oct.								
1.	19th.	11,000.	66.5.	30.0.	2.0.	1.5.		
3.	21st.	12,000.	64.5.	30.5.	3.0.	2.0.		

§ The numbers in these columns represent the cells of each class met with during the counting of 300 leucocytes daily.

CASE No.8. JAMES C. continued.

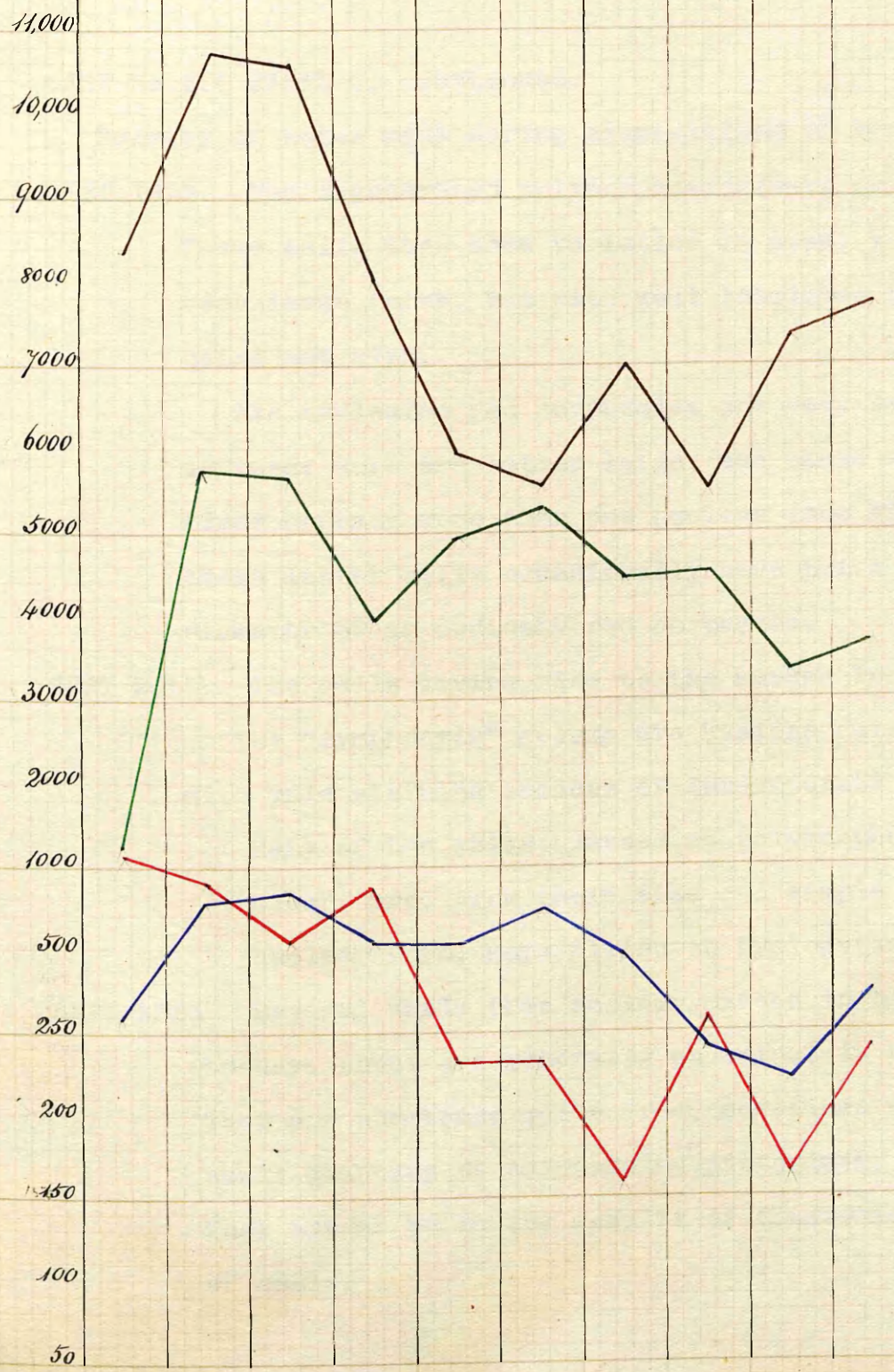
ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

Sept.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Total.
19.	8393.	1210.	297.	1100.	11,000.
20.	10679.	5738.	778.	905.	18,100.
21.	10470.	5636.	820.	524.	17,450.
22.	8000.	3980.	536.	884.	13,400.
23.	5856.	4932.	531.	231.	11,550.
24.	5499.	5265.	702.	234.	11,700.
26.	6989.	4422.	482.	157.	12,050.
28.	5460.	4515.	241.	284.	10,500.
Oct.					
1.	7315.	3300.	220.	165.	11,000.
3.	7740.	3660.	360.	240.	12,000.

CASE No. 8.
Day of Illness

7th	8th	9th	10th	11th	12th	14th	16th	19th	21st.

11,000
10,000
9000
8000
7000
6000
5000
4000
3000
2000
1000
500
250
200
150
100
50



CASE No.8. JAMES C. continued.

Summary of notes made during examinations of Blood.

SEPT 19th. Few degenerated polymorpho-nuclears present. These cells show some variation in size, some very large forms, but with well lobulated nuclei being met with.

The nucleated red corpuscles are very well defined; some are rather large, and these sometimes contain more than one nucleus (see Fig. 3.) these latter cells occasionally have twice the diameter of an ordinary red corpuscle.

SEPT 20th. The cells giving rise to the marked increase in the "lymphocyte" column are hyaline cells with pale staining nucleus of intermediate size.

Many of the cells classed as polymorpho-nuclear, are, from their size and simple nuclear form, more allied to Myelocytes.

SEPT 23rd. Several small free nuclear masses in blood to-day; these are generally spherical in form. They are sometimes quite free, sometimes with small quantity of surrounding protoplasm. They appear to be the results of fragmentation of cells.

SEPT 24th. Fragmentation products again noted, and of larger size so as to resemble lymphocytes with half a dozen neutrophile granules. More frequent evidences of polymorpho-nuclear degeneration. Vacuolation of many of the large hyaline cells noted.

GROUP 2. 3 CASES.

CASE No.9. FRANCIS C. aet. 32.

Patient came into Hospital late on the 6th day of illness (JULY 21st.), the eruption having been first noticed on the 19th. When seen on the 22nd JULY, the face presented a livid dusky appearance, most marked on the forehead, and sides of the neck. In these situations, there was an abundant crop of fine shotty congested papules. A bright red papular eruption, the elements of which were irregular in size, was present over the trunk and limbs. It was especially abundant over the back, and inner aspect of thighs and legs; moderately abundant over the chest, and scattered more sparsely over the abdomen. The eruption in places had a purpuric appearance and many of the papules could not be obliterated by pressure. The remains of a prodromal rash, in the form of an irregularly distributed livid mottling, were discernible in addition to the elements of the more permanent eruption. The eyes were suffused and congested; throat and mouth presented signs of congestion with fairly plentiful eruption. Slight delirium present on admission.

JULY 24th. Delirium has passed off. Facial eruption more prominent, causing discomfort from sense

of tension. Some of the eruptive elements on the face, as well as on the backs of the hands show early vesiculation.

JULY 25th. Vesiculation general over face, which is greatly swollen; the eyes practically closed by oedema. The eruption has reached the same stage over the hands, arms and chest; elsewhere however, it is still papular, the papules being surrounded by fiery red bases.

JULY 28th and 29th. Dessication and crusting have commenced in eruption on face. The eruption where vesicular, is rapidly drying, while many of the elements are receding having never developed beyond the papular stage. Turbidity of the vesicles, which never reached considerable dimensions, was not a general feature, and convalescence proceeded without any untoward event. This case is one therefore which commencing with the signs of a severe attack, "aborted" in the manner frequently seen in Variola.

CASE No.9. FRANCIS. C. continued.

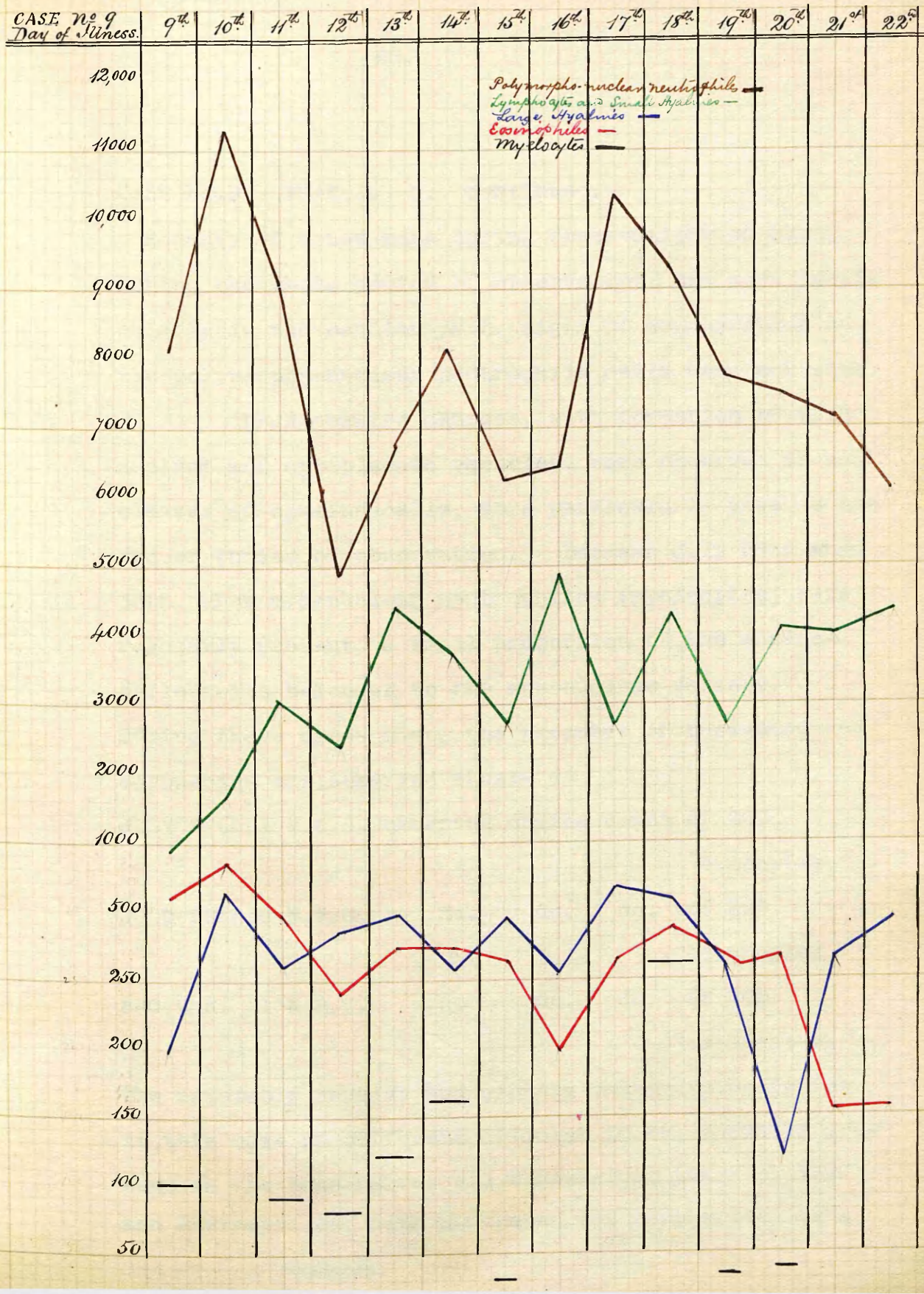
July. Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear. %	Lympho-cytes. %	Large Hya-lines. %	Eosino-philes %	Myelo cytes %
23. 8th.	8466.	81.0.	7.0.	8.0.	4.0.	
24. 9th.	9933.	81.7.	9.3.	2.0.	1.0.	1.0.
25. 10th.	14,425.	78.0.	11.7.	4.3.	6.0.	
26. 11th.	12,950.	70.0.	23.0.	2.3.	3.7.	.7.
27. 12th.	§8000.	60.7.	30.0.	5.3.	3.0.	1.0.
28. 13th.	13,133.	55.7.	36.3.	4.0.	3.0.	1.0.
29. 14th.	12,700.	64.4.	29.1.	2.3.	2.9.	1.3.
30. 15th.	9850.	63.7.	28.0.	4.7.	3.3.	.3.
31. 16th.	11,700.	54.7.	41.3.	2.3.	1.7.	
Aug.						
1. 17th.	14,100.	73.7.	19.3.	4.7	2.3.	
2. 18th.	14,850.	62.3.	28.7.	3.7.	3.0.	2.3.
3. 19th.	11,050.	70.3.	24.0.	2.7.	2.7.	.3.
4. 20th.	11,950.	62.3.	33.7.	1.0.	2.7.	.3.
5. 21st.	11,650.	61.7.	34.3.	2.7.	1.3.	
6. 22nd.	10,940.	55.0.	39.3.	4.3.	1.3.	

§ Estimation probably below the correct figure. Pipette barely filled after some trials.

CASE No.9. FRANCIS C. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Myelo-cytes.	Total.
24.	8115.	924.	198.	596.	100.	9933.
25.	11,251.	1688.	620.	866.		14,425
26.	9065.	3017.	298.	479.	91.	12,950
27.	4856.	2400.	424.	240.	80.	8000.
28.	6758.	4404.	485.	364.	122.	12,133
29.	8179.	3696.	293.	368.	164.	12,700
30.	6274.	2758.	463.	325.	30.	9850.
31.	6400.	4832.	269.	199.		11,700
Aug.						
1.	10,392.	2721.	663.	324.		14,100
2.	9251.	4262.	549.	445.	343.	14,850
3.	7768.	2652.	298.	298.	34.	11,050
4.	7445.	4027.	119.	322.	37.	11,950
5.	7188.	3996.	314.	152.		11,650
6.	6017.	4299.	470.	154.		10,940


CASE No. 9
Day of Illness.
9th.
10th.
11th.
12th.
13th.
14th.
15th.
16th.
17th.
18th.
19th.
20th.
21st.
22nd.
12,000
11000
10,000
9000
8000
7000
6000
5000
4000
3000
2000
1000
500
250
200
150
100
50
Polymorpho-nuclear neutrophiles
Lymphocytes and Small Hyalines
Large Hyalines
Eosinophiles
Myelocytes

CASE No.9. FRANCIS C. continued.

Summary of notes made during observations on Blood. During the whole period of observation, but more particularly in the earlier part, signs of degeneration of the polymorpho-nuclear neutrophile cells were met with.

Degenerative changes, with formation of both nuclear and cytoplasmic vacuoles, were observed in both classes of hyaline cells, more particularly towards the end of period of observation. Between July 27th and 30th, when mononuclear neutrophiles (myelocytes) were regularly present, a small proportion of the eosinophile cells belonged to the mononuclear variety. During these dates also, the presence of nucleated red corpuscles was observed thus:-

JULY 27th. 1 N.R.C. observed during count of 300 leucocytes.

JULY 28th. 6 N.R.C. do. do. do. of 300 leucocytes.

AUG. 2nd. 1 N.R.C. do. do. do. of 300 leucocytes.

The tolerably regular and closely related association in this case of different cellular types, normally present in the bone-marrow viz. mononuclear neutrophiles and eosinophiles, with nucleated red corpuscles, is a noteworthy feature.

CASE No.10. PETER F. aet. 25.

Admitted on 6th day of illness. The eruption on the Face is abundant, in places coalescent, and consists of small papules or early vesicles; some pustulation has occurred in eruption round the mouth. The face is greatly swollen. Eruption over trunk and limbs fairly abundant, and its elements consisting of papules for the most part, vary considerably in size. Any vesicles which are present here are thin, flat and ill-developed. Conjunctivitis and faucial catarrh with eruption, are also present.

SEPT 13th. Patient's general condition much improved, evidences of commencing dessication in facial eruption. The eruption elsewhere has remained small and the attack is evidently "aborting".

SEPT 17th. General condition very good. The face shows now only slight crusting, and remains of the eruption elsewhere are present as brownish stained low-set papules.

Convalescence proceeded steadily, but one or two small superficial abscesses formed between SEPT. 20th and 24th. on the lower limbs.

CASE No.10. PETER F. continued.

Sept.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear. %	Lympho-cytes. %	Large Hya-lines. %	Eosino-philes. %	Myelo-cytes. %
11.	6th.	11,850.	50.0.	40.7.	3.7.	4.6.	1.0.
12.	7th.	14,000.	52.0.	43.5.	.5.	4.0.	
13.	8th.	11,450.	57.5.	35.0.	3.0.	4.0.	.5.
14.	9th.	8475.	41.5.	40.0.	6.0.	6.0.	6.5.
17.	12th.	9850.	45.4.	46.3.	3.0.	2.0.	3.3.
18.	13th.	7750.					
20.	15th.	10,150.	51.3.	41.3.	3.3.	3.0.	1.0.
22.	17th.	6200.	62.2.	33.3.	3.0.	1.0.	.5.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

Sept.	11.	11,850.	5925.	4823.	438.	546.	118.
	12.	14,000.	7280.	6090.	70.	560.	
	13.	11,450.	6584.	4017.	343.	458.	48.
	14.	8475.	3517.	3390.	508.	508.	552.
	17.	9850.	4472.	4560.	295.	187.	336.
	18.	7750.					
	20.	10,150.	5207.	4192.	335.	304.	112.
	22.	6200.	3856.	2064.	186.	62.	32.


CASE No. 10.
Day of Illness
6th
7th
8th
9th
12th
15th
17th
Polymorpho. nuclear
Lymphocytes & Sm. Hyalines
Large Hyalines
Eosinophiles
Myelocytes
9000
8000
7000
6000
5000
4000
3000
2000
1000
500
350
300
250
200
150
100
50

CASE No.10. PETER F. continued.

Summary of notes made during observations on Blood. During the first few days of observation, the polymorpho-nuclear cells, besides showing degenerative changes, were frequently observed with nuclei of simpler form than usual. The variations in their size also suggested the intermediate or transitional character of many. During the last day or two of observation, these features were less evident.

Both classes of hyaline cells show changes similar to those previously described.

The Myelocytes in this case were large and well defined. They appear to have been most numerous in the blood during the period of pustulation.

Nucleated red corpuscles were observed during the earlier part of the period, more particularly on Sept. 11th and 14th.

CASE No.11. JOHN H. aet. 32.

This patient came under observation on the 8th day of illness, at which time he presented an abundant facial eruption consisting of vesicles and papules partly vesicular. Over the trunk and limbs it had the usual distribution, and was especially abundant over the back.

SEPT 14th. Over the face, which since admission to Hospital, has been markedly oedematous, pustulation has reached its acme. This feature of the eruption is also, generally, very distinct.

SEPT 16th. Dessication of eruption noted; most advanced on the face, but crust formation is proceeding over the body.

SEPT 20th. A slight rise of temperature last night and maintained to-day is explained by an acute follicular tonsillitis.

From Sept 22nd. till the close of observations on the Blood, convalescence was interrupted by the appearance of numerous superficial post-variolar abscesses.

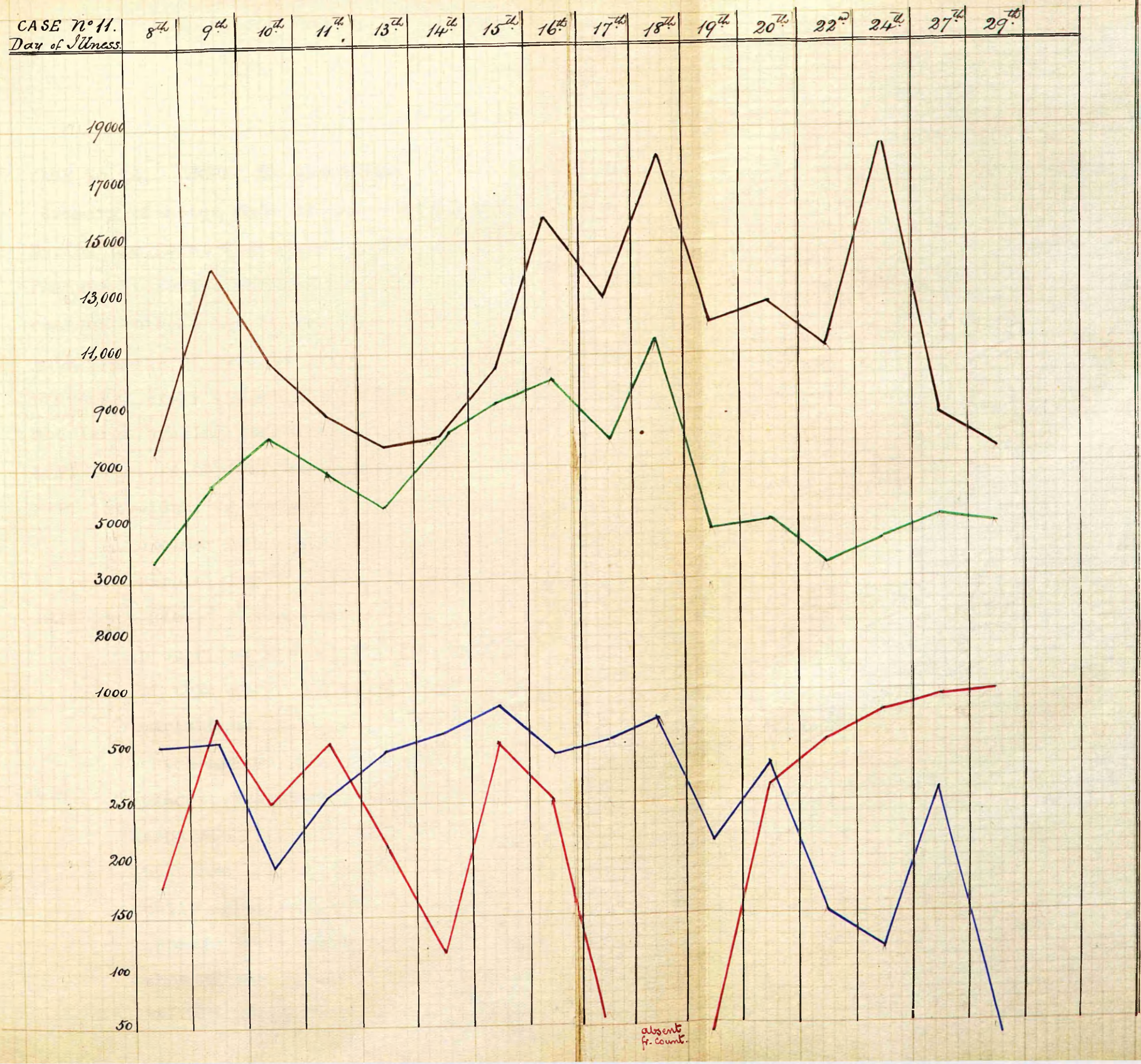
CASE No.11. JOHN H. continued.

Sept.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear. %	Lympho-cytes. %	Large Hya-lines. %	Eosino-philes. %	Myelo-cytes. %
12.	8th.	11,950.	62.5.	31.5.	4.5.	1.5.	
13.		21,500.	64.7.	29.0.	2.7.	3.6.	
14.		19,300.	55.7.	42.0.	1.0.	1.3.	
15.		16,367.	52.3.	42.7.	1.7.	3.3.	
16.							
17.		14,166.	55.0.	40.0.	3.5.	1.0.	
18.		16,950.	47.0.	48.7.	3.6.	.7.	
19.		21.100.	49.5.	44.0.	4.0.	2.5.	
20.		26,650.	59.6.	37.7.	1.7.	1.0.	
21.		21,450.	60.3.	36.7.	2.7.	.3.	
22.		29,950.	59.5.	38.0.	2.5.		
23.		17,150.	70.3.	27.7.	1.3.	.7.	
24.		18,450.	68.3.	27.7.	2.3.	1.7.	
26.		15,600.	72.5.	23.0.	1.0.	3.0.	
28.		23,650.	77.5.	18.5.	.5.	3.5.	
Oct.							
1.		15,150.	57.5.	34.0.	2.0.	6.5.	
3.		13,466.	56.3.	36.0.	.3.	7.3.	

CASE No.11. JOHN H. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

Sept.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Total.
12.	7469.	3764.	538.	179.	11,950.
13.	13910.	6235.	580.	775.	21,500.
14.	10750.	8106.	193.	251.	19,300.
15.	8560.	6989.	278.	540.	16,367.
17.	7791.	5666.	496.	213.	14,166.
18.	7966.	8254.	610.	120.	16,950.
19.	10,444.	9284.	844.	528.	21,100.
20.	15,883.	10,047.	452.	267.	26,650.
21.	12,934.	7872.	579.	65.	21,450.
22.	17,820.	11,381.	749.		29,950.
23.	12,056.	4840.	223.	31.	17,150.
24.	12,601.	5100.	424.	325.	18,450.
26.	11,310.	3588.	156.	546.	15,600.
28.	18,329.	4375.	118.	828.	23,650.
Oct.					
1.	8711.	5151.	303.	985.	15,150.
3.	7581.	4848.	40.	997.	13,466.


CASE N°11.
Day of Illness.
8th
9th
10th
11th
13th
14th
15th
16th
17th
18th
19th
20th
22nd
24th
27th
29th
19000
17000
15000
13,000
11,000
9000
7000
5000
3000
2000
1000
500
250
200
150
100
50
absent fr. count.

CASE No.11. JOHN H. continued.

Summary of notes made during observations on Blood. During the first four days of observation the chief feature presented was the presence of degenerative changes both in the polymorpho-nuclear neutrophiles and both classes of hyaline cells. The latter, as usual, presented every gradation of size between the lymphocyte and large hyaline varieties.

SEPT 17th. A typical Myelocyte found.

SEPT 15th-18th. A certain proportion of the polymorpho-nuclear cells are of "transitional" type with simple, imperfectly lobulated nuclei.

SEPT 18th-21st. The polymorpho-nuclear cells in larger proportion diverge from the typical characters of this cell. (1) in showing very distinct variations in size; (2) in possessing nuclei which are perhaps indented in two or three places, but whose component masses are not separated to anything like the extent exhibited by normal cells of this class. Their neutrophile granules however are both numerous and capable of staining well. The characters of some of the larger of these cells would almost warrant their being regarded as Myelocytes.

SEPT 20th. A Myelocyte of typical character observed to-day.

It is of interest to note the coincidence of the increase in the absolute numbers of the polymorpho-nuclear leucocytes on this as well as subsequent dates, with the development of follicular tonsillitis and later of post-eruptive abscesses. With the wane of the polymorpho-nuclear leucocytosis during the last two days of observation, the leucocytic formula more characteristic of Variola begins to re-appear.

It must be added that no nucleated red corpuscles were recorded during the observation of this case.

GROUP 3.

A Summary of the post-mortem reports of these cases is appended at the close.

CASE No.12. JAMES M. aet.52.

Admitted to Hospital on the 4th day of illness with the commencing eruption of what promises to be a very severe attack of Smallpox. The face is dusky and livid; an abundant, practically confluent crop of fine papules is scattered over the face, scalp and neck, while the eruption is also abundant in the mouth, fauces, tonsils and tongue.

A similar confluent papular eruption is present over the arms and hands. Over the trunk, the eruption, as yet discrete, is nevertheless very abundant.

JULY 10th. The facial eruption now consists of confluent small low-set vesicles; the eruption on the hands and arms, confluent from the first, is also vesicular. That on the inner aspects of the thighs is in a similar condition, while over the trunk it is semi-confluent.

JULY 11th. The eruption has undergone further vesiculation over the face which is now greatly swollen. The contents of the greater portion of the vesicles, which are not well developed, have

become turbid. The eruption has become confluent on the back, arms and legs, and, except in the latter situation its elements are flat and irregular.

JULY 12th. The eruption is now fully pustular. (Note. The presence of Staphylococci was determined in this case, ante-mortem in the contents of the pustules and post-mortem in the Spleen and Bone-marrow- See respective Sections). It has formed large irregular patches by coalescence. Some signs of dessication on forehead. Patient critically ill.

JULY 13th. There is a practically confluent suppurative infiltration of the tissues of scalp and face. Over the trunk and limbs, the eruption, confluent over large areas, is represented by an almost continuous puriform infiltration of the epidermis and where more discrete, by small flat yellow pustules.

JULY 14th. Patient extremely ill; slight delirium; high fever. Face and scalp entirely undermined by pus. An offensive odour is emitted from the surface. The sero-purulent crusts which have formed over the wrists etc have fractured, exposing raw ulcerated surfaces.

JULY 15th. Patient died at 4-20 a.m. to-day.

CASE No.12. JAMES M. continued.

July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.	Myelo-cytes %.
8.	4th.	12,200.	70.3.	13.7.	.4.	1.3.	14.3.
9.	5th.	15,700.	56.3.	9.7.	1.3.	4.0.	28.7.
10.	6th.	22,200.	43.0.	7.7.	1.6.	3.6.	44.1.
11.	7th.	11,933.	36.4.	14,8.	2.0.	5.2.	41.6.
12.	8th.	9866	32.1.	13.0.	.84.	9.58.	44.52.
13.	9th.	7766.	21.3.	8.7.	.7.	2.6.	66.6.
14.	10th.	7733.					

Excluding the Myelocytes, the following per centage numbers are obtained.

July 8th.	82.1.	15.9.	.4.	1.5.
9th.	78.9.	13.5.	1.87.	5.6.
10th.	75.7.	13.6.	2.9.	7.8.
11th.	62.3.	25.4.	3.4.	8.9.
12th.	58.0.	23.3.	1.5.	17.2.
13th.	64.0.	26.0.	2.0.	8.0.

CASE.No.12. JAMES M. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Myelo-cytes. & Transitional Forms of Polym.	Total.
8.	8576.	1671.	48.	158.	1747.	12,200.
9.	8839.	1523.	204.	628.	4506.	15,700.
10.	9501.	1718.	355.	799.	9827.	22,200.
11.	4333.	1754.	238.	620.	4988.	11,933.
12.	3167.	1282.	78.	947.	4392.	9866.
13.	1654.	675.	54.	202.	5181.	7766.

Summary of notes made during observations on Blood.

JULY 8th. A considerable number of transitional forms of polymorpho-nuclear neutrophiles are met with, in which the nucleus is very imperfectly lobulated. Degenerated examples of these cells as well as of the lymphocytes occur. 3 nucleated red corpuscles observed today. Occasional products of fragmentation of polymorpho-nuclear cells are met with. The frequent occurrence of groups of blood-platelets is noted.

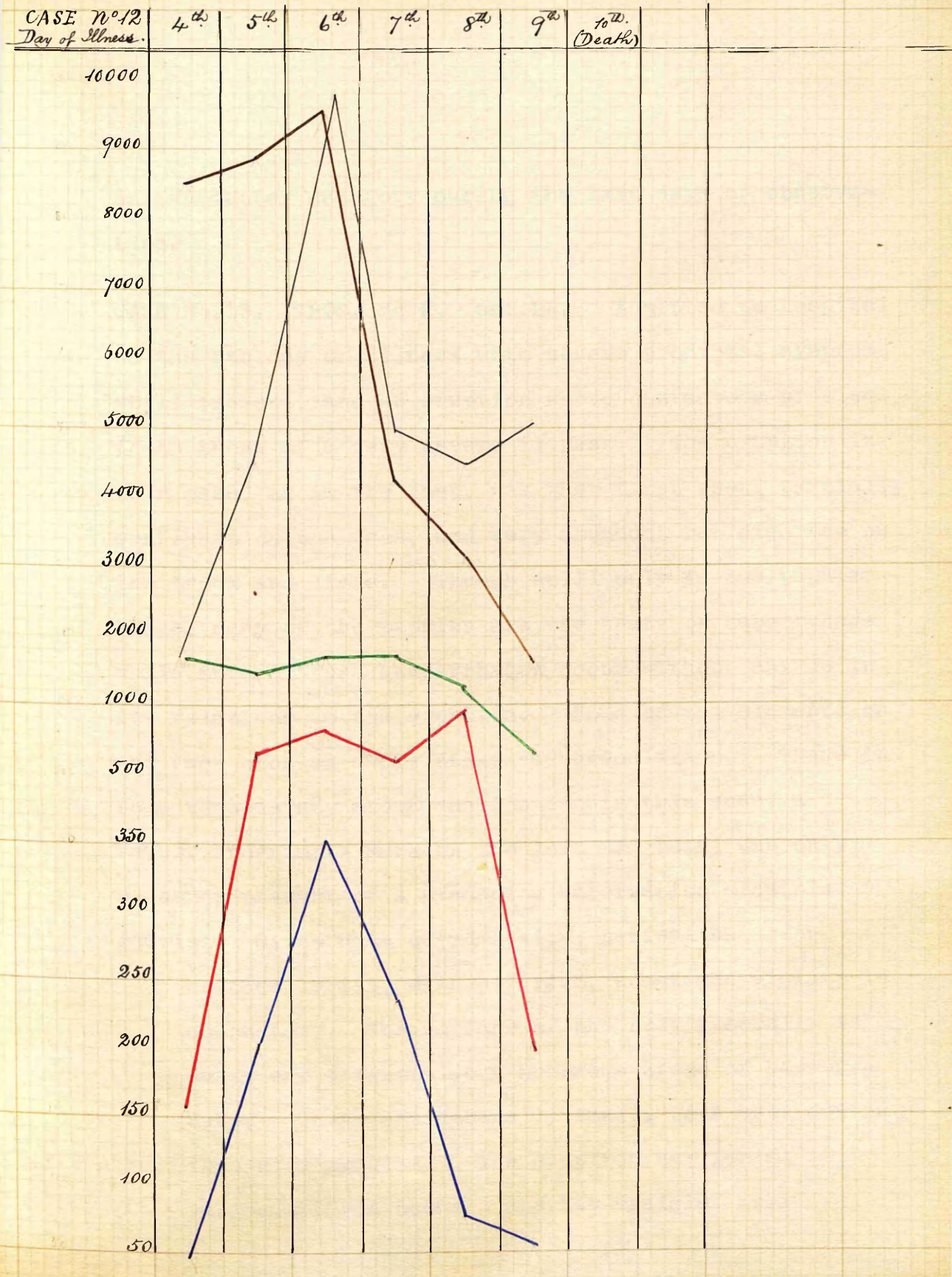
JULY 9th. Considerable numbers of neutrophile cells are met with whose nucleus is of simple, imperfectly lobulated form. 4 nucleated red corpuscles observed.

JULY 10th. Transitional forms of neutrophiles still numerous. 2 nucleated red corpuscles observed.

JULY 11th. Degenerated and transitional forms of the neutrophile cells are common. Degenerative changes are noted in both mono- and poly-nuclear neutrophile cells. The relative frequency of nucleated red corpuscles in the blood is indicated by the fact that no less than 19 of these elements were encountered whilst counting 340 leucocytes.

JULY 12th. No change exists in condition of neutrophile elements; the occurrence of a well lobulated polymorpho-nuclear neutrophile is rare. Some of the eosinophile cells seen to-day are of mono-nuclear type. 5 nucleated red corpuscles found while counting 355 leucocytes.

JULY 13th. The well lobulated polymorpho-nuclear neutrophiles are now more reduced than ever. Correspondingly, the number of cells of this class in which the nucleus shows just an indication of commencing polymorphism is greatly increased. These, which in the tables, have been reckoned as Myelocytes, in view of the fact that they conform less to the characters of the polymorpho-nuclear, than to those of the mono-nuclear neutrophiles, serve to explain the high figures


CASE N°12
Day of Illness.
4th.
5th.
6th.
7th.
8th.
9th.
10th.
(Death)
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
500
350
300
250
200
150
100
50

in the latter category during the last days of observation.

CASE No.13. THOS. Mc K. aet.28. Admitted to hospital on the 5th day of illness with severe prodromal symptoms still present, and an eruption whose characters promise to be those of a very severe illness. The eruption in this case, as in the last, was when first seen, partially confluent on the face, and very abundant but discrete on the trunk and limbs. Though still only in the papular stage, many of the papules are the seats of haemorrhage, while more diffuse haemorrhages occur without any definite relations to the eruption. Some of the elements on the face show an early stage of vesiculation. There is some uncertainty about vaccination in this case, a rather indefinite mark on the left arm being the only evidence present of a prededing vaccination cicatrix.

AUG.1st. Since date of admission, patient has been critically ill, with delirium, sometimes violent in character. The surface of the body generally is dusky and presents very numerous areas of haemorrhage. These are generally small, with well defined irregular margins. The eruption has become vesicular, but nowhere are the vesicles well

developed. They are small, flattened and irregular in form, while many contain blood. Others contain only a slightly turbid serum.

AUG.3rd. Patient died this morning at 7-30.

July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.	Myelo-cytes %.
28.	6th.	9433.	80.0.	9.0.		1.0.	10.0.
29.	7th.	10,200.	70.5.	10.8.	3.1.	4.0.	11.6.
30.	8th.	11,050.	60.0.	13.2.	4.06.	.71.	22.03.
31.	9th.	15,450.	46.5.	12.6.	.33.	.67.	39.9.
Aug.							
1.	10th.	7050.	37.2.	30.0.	5.6.	5.6.	21.6.
2.	11th.	3100.	25.0.	39.0.	2.5.	2.0.	31.5.

After exclusion of myelocytes, the per centage figures obtained are the following.

July 28th.	88.9.	10.0.		1.1.
July.29th.	79.8.	12.2.	3.4.	4.6.
July 30th.	76.4.	16.8.	5.9.	.9.
July 31st.	77.3.	21.0.	.55.	1.1.
Aug.1st.	47.4.	38.2.	7.1.	7.1.
Aug.2nd.	36.5.	56.9.	3.65.	2.9.

CASE No.13. THOMAS Mc K. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Myelo-cytes.	Total.
28.	7546.	849.		94.	944.	9433.
29.	7191.	1091.	316.	408.	1194.	10,200.
30.	6630.	1458.	44.	77.	2841.	11,050.
31.	7184.	1946.	51.	103.	6166.	15,450.
Aug.						
1.	2622.	2115.	395.	395.	1523.	7050.
2.	775.	1209.	77.	62.	977.	3100.

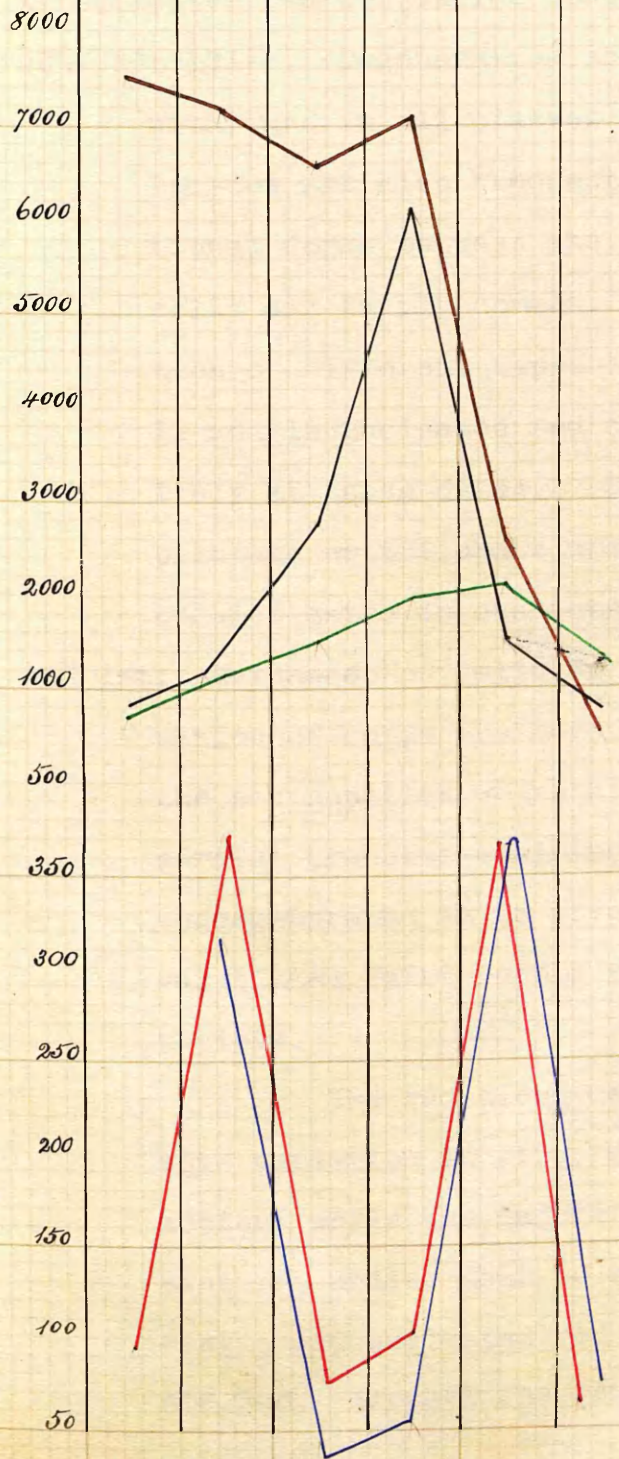
Summary of notes made during ibservations on the Blood.

JULY 28th. Many of the polymorpho-nuclear neutrophiles show degenerative changes. Vacuolation and deficiency of nuclear stain in these cells is often a marked feature. Fragments of free nuclei or portions of cells with fragmented nuclei are occasionally found. These are in many instances sufficiently characteristic to permit of the observation that they are derived both from neutrophiles and lymphocytes. 2 nucleated red corpuscles observed to-day.

JULY 29th. The degenerative changes noted above are present and in addition the eosinophile cells partake in the retrograde changes.

CASE N° 13.

Day of Illness	6th	7th	8th	9th	10th	11th	12th (Death)



17 nucleated red corpuscles observed while counting to-day

JULY 30th&31st. Degenerative changes more frequently met with, and in all classes of leucocytes. The myelocytes are also frequently degenerated. Transitional forms between the two classes of neutrophile cells are fairly common. Products of fragmentation of different types of cells are not infrequent 11 and 13 nucleated red corpuscles noted respectively at these dates. Some of these cells possess bilobate or trilobate nuclei, and are distinctly megaloblastic in character.

AUG.1st. Evidences of cellular degeneration and fragmentation of cells are more marked to-day. Many of the neutrophiles of both classes present only partial granular staining. Some of the cells are so degenerated as to give merely a homogeneous or vacuolated faint purple stain with no evidence of nucleus.

The red blood corpuscles exhibit to-day some variation in size, as well as in staining reaction; while the majority are of the usual orange tint not unlike that of the nucleated red corpuscles. 10 nucleated red corpuscles seen to-day.

AUG.2nd. Amongst the leucocytes, the great

reduction in which is at once apparent in the films) many are so degenerated that it is almost impossible to tell their nature. Some are full of vacuoles and show only a trace of nuclear staining. Products of fragmentation of cells are very numerous. Examples of mono-nuclear eosinophile cells are present to-day. Some of these, as well as the mono-nuclear neutrophiles are either dwarfed or fragmented. The facts noted yesterday with reference to the red blood corpuscles are present to-day. 18 nucleated red corpuscles are met with, and these include both normoblasts and megaloblasts in approximately equal numbers.

AUG.3rd. Films of blood taken post-mortem show very few degenerated polymorpho-nuclear and mono-nuclear neutrophiles. Lymphocytes are more frequently met with than any other forms of leucocytes.

CASE No.14. ALEX. C. aet.35.

The illness commenced with severe prodromal symptoms during which a prodromal rash appeared consisting of irregular maculae of deep red colour. Along the adductor aspects of the thighs, the rash was distinctly haemorrhagic in character. The more permanent eruption was, on admission, felt rather than seen, as a closely set crop of fine papules. During the development of the eruption,

several areas of haemorrhage appeared in the skin of the chest and abdomen.

SEPT 13th. The eruption has assumed a more haemorrhagic character, especially over the chest and legs. Temperature high with delirium at night.

SEPT 17th. The eruption which is confluent on the face, and incompletely so over the trunk and limbs shows little progressive tendency. The vesicles or pustules (both are present) are small and ill-formed with dusky haemorrhagic areolae. The centres of many are also black in colour from the presence of altered blood. General condition very weak with poor pulse, delirium slight but constant.

SEPT 19th. The face is covered by an almost continuous crust of dark brown colour. Elsewhere, the eruption is in the form of flat pustules which do not show any progress. Patient is extremely weak and delirious. No blood was obtainable after puncture of the skin, and patient died on the following day.

CASE No.14. ALEX. C. continued.

Sept.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %	Lympho-cytes %	Large Hya-lines %	Eosino-philes %	Myelo-cytes %
11.	6th.	11,700.	84.0.	10.35.	2.3.	1.0.	2.35.
12.	7th.	11,600.	73.7.	15.3.	4.7.	5.3.	1.0.
13.	8th.	15,700.	65.4.	20.2.	5.3.	2.6.	6.5.
14.	9th.	20,150.	61.5.	21.5.	6.5.	9.0.	1.5.
15.	10th.	17,600.	67.03.	18.5.	3.03.	7.9.	3.54.
17.	12th.	5250.	49.0.	29.5.	5.0.	9.5.	8.0.
18.	13th.	7833.					

The percentage numbers calculated after exclusion of myelocytes are as follows.

Sept. 11th.	86.00.	10.58.	2.38.	1.04.
12th.	74.7.	15.3.	4.7.	5.3.
13th.	69.79.	21.6.	5.7.	2.91.
14.	62.4.	21.8.	6.67.	9.13.
15.	69.59.	19.12.	3.13.	8.16.
17.	53.2.	32.07.	5.43.	9.3.

CASE No.14. ALEX. C. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

Sept.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Myelo-cytes.	Total.
11.	9828.	1217.	269.	117.	269.	11,700.
12.	8549.	1775.	545.	615.	116.	11,600.
13.	10,268.	3171.	832.	424.	1005.	15,700.
14.	12,392.	4332.	1310.	1813.	303.	20,150.
15.	11,792.	3256.	528.	1408.	616.	17,600.
17.	2572.	1549.	262.	499.	368.	5250.

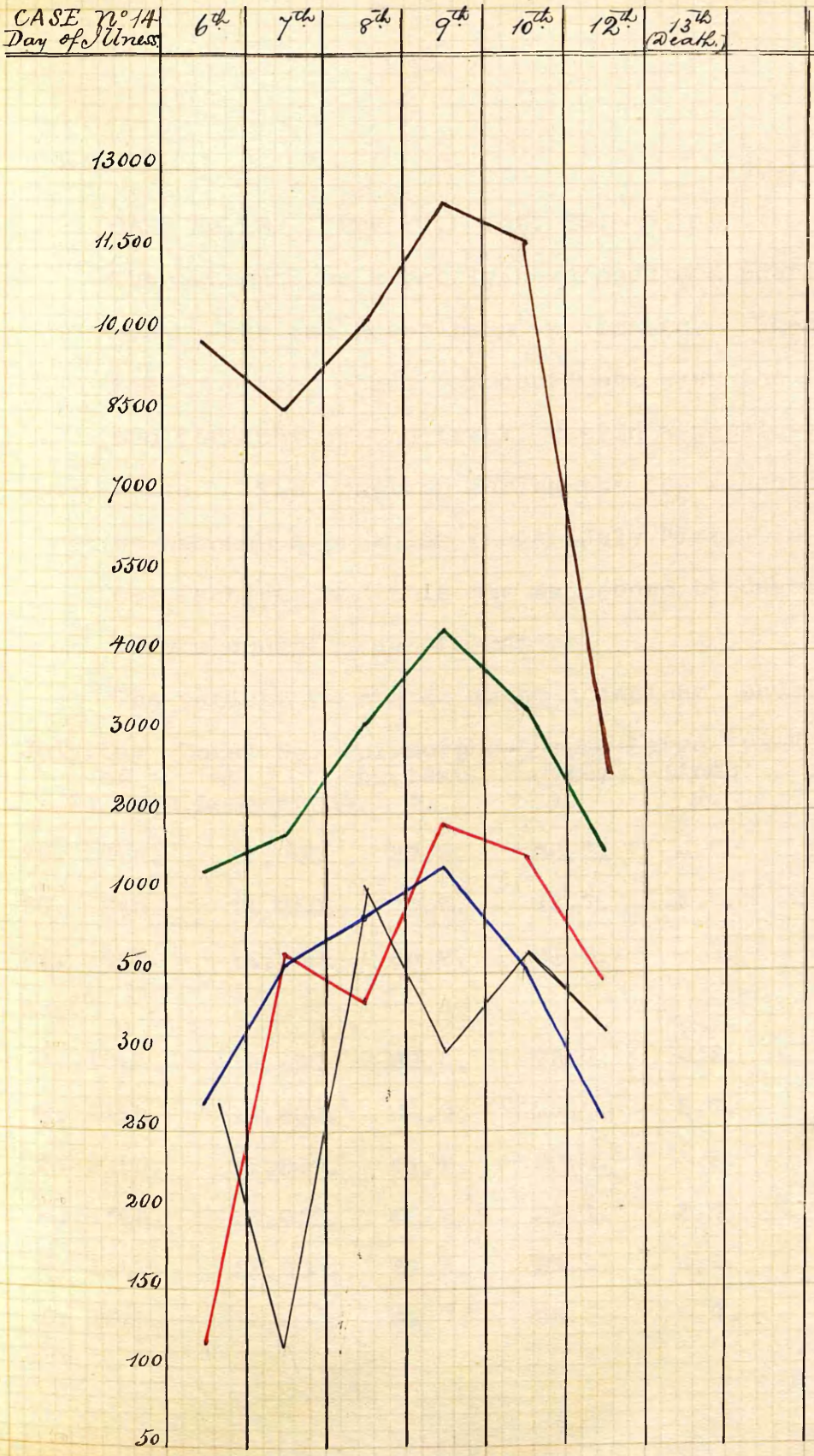
Summary of notes made during observations of Blood.

SEPT 11th&12th. Degenerative changes present in neutrophile cells of both classes and granular staining is very defective in them. Transitional forms common. Two nucleated red corpuscles seen on latter date.

SEPT 13th. Three nucleated red corpuscles found.

SEPT 14th. Degenerative changes on this and subsequent dates more marked than formarly. The character of these changes is similar to that described in the two previous cases. Probably a greater proportion of neutrophile cells with single indented nuclei might be placed amongst the "Myelocytes" than the number represented by 1.5%.

SEPT 15th&17th. 3 nucleated red corpuscles observed on each of these dates.


CASE N° 14
Day of Illness
6th
7th
8th
9th
10th
12th
13th (Death.)
13000
11,500
10,000
8500
7000
5500
4000
3000
2000
1000
500
300
250
200
150
100
50

CASE No.15. Mrs T. aet. 35.

The patient was a poorly developed and poorly nourished woman, who had never been vaccinated. When first seen, the eruption, which was confluent over the face, neck and portions of the trunk, was in a papulo-vesicular stage. The eruption during the few succeeding days passed through a pustular stage (July 31st.) in fairly typical fashion, and this was succeeded by dessication with very abundant crust-formation.

The patient recovered after a tedious convalescence.

July.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large Hya-lines %.	Eosino-philes %.	Myelo-cytes %.
29.	7th.	11,900.	67.3.	26.3.	4.7.	.7.	1.0.
30.	8th.	11,250.	79.3.	13.7.	3.7.	2.3.	1.0.
31.	9th.	14,750.	66.2.	21.0.	4.5.	6.8.	1.5.
Aug.							
1.	10th.	12,450.	69.4.	22.7.	4.6.	.7.	2.6.
2.	11th.	14,800.	64.0.	25.7.	5.7.	1.6.	3.0.
3.	12th.	11,800.	61.2.	29.4.	3.2.	1.8.	4.4.
4.	13th.	10,950.	65.4.	28.1.	3.6.	1.1.	1.8.
5.	14th.	13,300.	69.3.	23.4.	4.1.	.8.	2.4.
6.	15th.	11,400.	62.7.	28.3.	5.7.	.3.	3.0.

CASE No.15. Mrs T. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

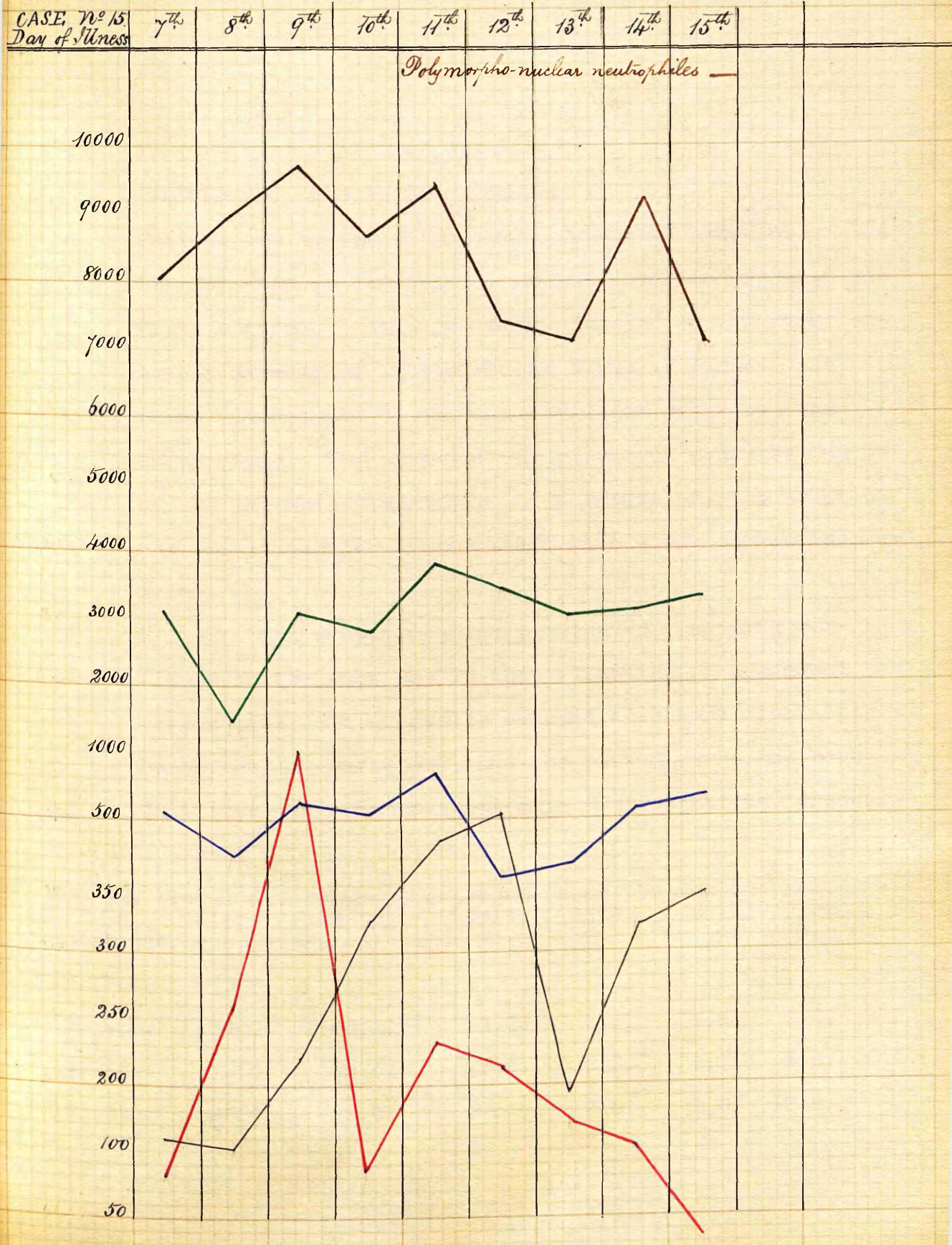
July.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Myelo-cytes.	Total.
29.	8009.	3130.	559.	83.	119.	11,900.
30.	8921.	1541.	416.	259.	113.	11,250.
31.	9764.	3097.	664.	1003.	222.	14,750.
Aug.						
1.	8640.	2826.	573.	87.	324.	12,450.
2.	9472.	3803.	843.	237.	445.	14,800.
3.	7221.	3469.	377.	212.	521.	11,800.
4.	7161.	3077.	394.	120.	198.	10,950.
5.	9217.	3112.	545.	106.	320.	13,300.
6.	7148.	3226.	650.	34.	342.	11,400.

Summary of notes made during examinations of Blood.

JULY 29th. 8 nucleated red corpuscles found in counting 300 leucocytes. Majority of polymorpho-nuclear cells shows signs of degeneration. Considerable proportion of transitional forms.

JULY 30th. 2 nucleated red corpuscles observed.

JULY 31st. The extent of the degenerative changes in the polymorpho-nuclear cells is greater than before. Similar changes are also present in both varieties of hyaline cells, but not to the same extent.


CASE. No 15
Day of Illness
7th
8th
9th
10th
11th
12th
13th
14th
15th
Polymorpho-nuclear neutrophiles
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
500
350
300
250
200
100
50

CASE No.16. Mrs Mc K. aet.49.

Patient was seized with severe prodromal symptoms on the 8th Oct. and on the morning of the 11th the eruption was first noticed. This was most abundant on the face, extensor aspects of fore-arms and backs of hands. In these situations, it was not confluent and free from haemorrhage. The eruption was plentiful over the fauces and buccal mucous membrane. On admission, the eruption was mainly papular in character with a few commencing vesicles.

The eruption quickly extended, becoming confluent on the face and in this situation of a general purple tint. It gradually assumed elsewhere distinctly haemorrhagic characters, and the patient, who had been delirious since the haemorrhagic manifestations, gradually sank.

Oct.	Day of Illness.	Total No. of Leucocytes.	Polymorpho-nuclear %.	Lympho-cytes %.	Large lines %.	Hya- %.	Eosino-philescytes %.	Myelo- %.
12.	5th.	7300.						
13.	6th.	13000	66.2.	23.1.	3.5.	4.8.	2.4.	
14.	7th.	7200	62.0.	19.5.	6.5.	5.0.	6.5.	
15.	8th.	6550.	33.0.	47.0.	7.0.	1.0.	12.0.	

CASE No.16. Mrs Mc K. continued.

ABSOLUTE NUMBERS OF DIFFERENT VARIETIES OF LEUCOCYTES.

Oct.	Polymorpho-nuclear.	Lympho-cytes.	Large Hya-lines.	Eosino-philes.	Myelo-cytes.	Total.
12.						7300.
13.	8606.	3003.	455.	624.	312.	13000.
14.	4500.	1404.	468.	360.	468.	7200.
15.	2161.	3078.	458.	65.	788.	6550.

Summary of note made during examinations of Blood.

The changes noted in this case in the white cells were similar to those mentioned in the previous cases of this group. The number of fragmentation forms, chiefly of the polymorpho-nuclear cells was considerable. Degeneration of these cells was marked, and similar changes were observed in the other classes of cells.

Oct 13th. 3 or 4 nucleated red corpuscles observed.

14th. 6 do. do. do. do.

15th. about 20 observed during count. A fair proportion of these, as well as of those noted yesterday, were of megaloblastic character.

The following are abstracts of the post-mortem features of Cases Nos. 12, 13 & 14:-

CASE No.12. JAMES M.

The body of a powerfully built and well-nourished man. The entire surface is covered by a profuse variolar eruption, confluent on the face and neck, semi-confluent elsewhere. On the face there is most extensive crusting. Elsewhere, the eruption is fully pustular.

All the organs show extreme softening from post-mortem changes. The Heart muscle is very soft. Valvular apparatus healthy. Both lungs exhibit a moderate degree of anthracosis and emphysema. They present no other noteworthy condition. The Liver is enlarged, soft and generally fatty. Spleen is enlarged and congested its pulp soft (almost diffluent). The remaining abdominal viscera present nothing of note. The rib-marrow is red and of rather fluid consistence.

CASE No.13. THOMAS Mc KECHNIE.

The face, neck and upper part of the body generally is covered with a confluent eruption of variolar pustules, the individual elements which are discerned in places being very small. Here and there, haemorrhage has occurred into certain of the elements, and partial crusting is visible on the face. Over the lower parts of the

body, the eruption although very abundant, is not quite confluent; it presents generally the same characters as in other parts, but over the legs and feet it is distinct ly petechial in character.

The pericardium is free from haemorrhages. The Heart whose valvular apparatus is normal, presents a homogeneous cloudy appearance of its muscle. The Lungs are very congested and oedematous, several areas of haemorrhage being observed in their lower lobes. There are also numerous small subpleural haemorrhages over their diaphragmatic surfaces.

Spleen is considerably enlarged, congested and firm. The Liver is enlarged, congested and presents appearances due to cloudy swelling. Kidneys are in a similar condition. The Stomach and Intestines are greatly congested and small areas of haemorrhage are present in both.

CASE No.14. ALEX. C.

The entire surface is the seat of a very profuse variolar eruption, in a late pustular stage, the individual elements being flat and ill-developed. Over the lower part of the face, there is extreme crusting.

The Heart presents no condition unusual to the disease. There are no haemorrhages. There are patches

of greyish consolidation with the characters of broncho-pneumonia in both Lungs. The Spleen is small, firm and its pulp is of rather atrophied appearance. The Liver is slightly enlarged, and presents a moderate degree of fatty infiltration. The Kidneys are congested and exhibit in marked degree appearances due to cloudy swelling. Haemorrhages are frequent in Mesentery, Stomach and Intestines, the latter being much congested.

SINGLE OBSERVATIONS IN SEVERE CASES.

The following single observations on the blood shortly before death in 3 cases (2 haemorrhagic and 1 confluent with haemorrhages) were made with the view of confirming the presence of and obtaining further data as regards the proportions of Myelocytes present in such cases.

CASE 17. JOHN B.

Patient is a muscular well-developed man. The face is deeply congested and covered by a fine badly developed eruption. Subconjunctival haemorrhage is so abundant as to entirely conceal the sclerotics. The body is covered by a petechial eruption which is almost confluent on the back between the shoulders. Lower limbs present numerous areas of haemorrhage bright red in colour and with irregular crenated edges.

Evening temperature on day of observation (25th February 1901) was only 99° F. but there was marked delirium, rapid poor pulse etc and patient died about 36 hours after examination.

Total No. Leucocytes.	Polymorpho-nuclear%.	Lympho-cytes%.	Large Hya-lines%.	Eosino-philes%.	Myelo-cytes%.
13,950.	54.3.	25.7.	9.3.	.7.	10.0.

These figures represent the following Absolute numbers respectively

7575.	3585.	1297.	97.	1396.

The polymorpho-nuclear cells show great variations in size. Many of the larger especially are of transitional type. Some are extensively altered by vacuolation. Several results of cell-fragmentation are observed; these most frequently are represented by small masses of protoplasm about the size of a red corpuscle, filled with neutrophile granules and without a nucleus or portion of one.

CASE 18. Mrs S.

Patient admitted on 5th day of illness with an abundant eruption in the form of small purple petechiae. Face slightly swollen and congested but free from haemorrhages as are also the eyes. The examination of the blood was made just 12 hours before death.

Total No. of Leucocytes.	Polymorpho-nuclear %	Lympho-cytes %	Large Hya-lines %	Eosino-philes %	Myelo-cytes %
2450.	45.5.	34.3.	6.4.	4.8.	9.0.
These figures represent the following Absolute numbers:-					
	1115.	840.	157.	117.	221.

The general characters of the cells are similar to those noted in previous cases of the same kind. 7 nucleated red corpuscles were seen during examination.

CASE No.19. DAVID P. aet. 33.

Admitted to Hospital on the 8th day of illness with an abundant eruption of marked haemorrhagic character. Amongst the subcuticular haemorrhages are a few imperfect ly developed vesico-pustules. The blood was examined on the 11th day of illness and patient died the following day.

Total No. of Leucocytes - 7430.

Polymorpho-nuclear neutrophiles and transitional forms of these cells.	74.4%
Lymphocytes and Small Hyalines.	5.5%
Large Hyalines.	4.2%
Eosinophiles.	4.6%
Mononuclear neutrophiles.	11.3%

The corresponding Absolute numbers are as follows:-

5528. 408. 312. 342. 840.

Only one or two nucleated red corpuscles are met with. A good many examples of cell-fragmentation however are seen, chiefly of the neutrophile variety. The small percentage of lymphocytes and cells of this class present on this occasion is an exceptional feature in the blood in Variola.

CONCLUSIONS REGARDING the BLOOD in VARIOLA.

A general survey of the results of enumeration of the leucocytes contained in the foregoing observations shows that Variola in all its clinical forms is accompanied by leucocytosis. This differs considerably in degree in the various types of cases, and even in cases agreeing in their general characteristics, but in all, the character of the leucocytosis as exhibited by differential enumeration, remains practically the same.

The feature which characterises it, in distinction from that which is found to accompany the majority of the acute exanthemata, is that it is mononuclear and not polymorpho-nuclear in character. In other words, the condition is one in which the smaller mononuclear hyaline cells (including the lymphocytes) are increased at the expense of the polymorpho-nuclear elements.

I shall first of all review the general facts in connection with each of the foregoing groups of cases, and afterwards note the manner in which each of the varieties of leucocytes and associated cells have appeared to me to be implicated in the disease - process.

In the greater number of the cases in Group 1. leucocytosis was already present when the patients came under observation (5th to 7th days of the disease). In

one or two however, (Nos. 4 and 6) the observations were commenced prior to the declaration of leucocytosis.

In the mildest cases, leucocytosis is not established until the rash has manifested itself, and attains a moderate acme either at the period when the majority of the elements have become turbid or even at a later stage. Speaking generally however of the cases in this group, it may be said that leucocytosis, commencing either at, or slightly before, the appearance of the eruption, attains a maximum at the 8th or 9th day (when turbidity of the vesicles is most general) and that it very slowly declines from this date onwards. With the supervention of suppurative or other inflammatory phenomena during convalescence it may undergo a subsequent rise which only exceptionally however exceeds the degree present on the 8th day.

Group 2. The facts correspond in all important particulars with those detailed above in connection with group1. As illustrated by cases Nos.9 and 11, a comparatively high rate of leucocytosis is maintained sometimes till late in the illness, when dessication and crusting have become general. In case No.11 the rise in leucocytosis during the recession of the eruption may be referred to the attack of acute tonsillitis noted.

Group 3. As noticed in the introduction to this section

the existence of leucocytosis is doubted by certain investigators in the most severe types of Variola. My observations lead however to the inference that a moderate but transient leucocytosis exists even in these cases. It appears as if the attempt were made to realise the curve of leucocytosis characteristic of more favourable cases of Variola, but that the reaction of the haematopoietic organs and tissues suddenly and significantly fails, with a correspondingly abrupt fall of leucocytes before death. Thus in two cases (Nos.13 and 14) a moderate leucocytosis was reached on the 9th day before the rapid ante-mortem reduction made its appearance. In two others (Nos.12 and 16) the feeble reaction of the haematopoietic organs is indicated before the leucocytosis had reached its acme.

The contrast offered by the course of the leucocytosis in Case No.15 (recovery after severe attack in unvaccinated subject) is sufficiently striking, being well maintained during the period of observation.

An analysis of the modifications, both in number and characters, of the various leucocytes and associated cells also reveals many features of interest. These are noted in connection with each type of cell in the following statement:-

POLYMORPHO-NUCLEAR NEUTROPHILE LEUCOCYTE.

This, the most numerous of all the varieties of leucocyte in normal blood, undergoes in Variola, a marked relative reduction, the proportion being frequently no more than 46 - 50% of all the cells present. Exceptionally even in the mild cases of Group 1, the proportion has been observed to fall as low as 33-36%. Generally speaking, it is on the 8th or 9th day of the disease that the greatest relative (and generally absolute) reduction has been observed to occur - at the same date, as will be seen later, as that at which thelymphocytes and smaller hyaline cells show the greatest increase. This relative reduction of thepolymprpho-nuclear cells continues for a considerable time - till after the 20th day of illness at least. It must be noticed however, that this relative reduction, in view of the total numbers registered, corresponds with an absolute increase - a point which seems to have been somewhat lost sight of in similar researches.

Only in four cases (Nos.5,9,13,14,) was both a relative and absolute increase in this type of cell noted. This state of matters, noticed on the 6th, 7th and 8th days of the disease in these cases however, was speedily replaced by the more usual condition viz. a great relative reduction.

A similar state of matters has, exceptionally, come under observation during convalescence, as the result of inflammatory affections (Case No.11).

Further, degenerative changes appear to overtake this class of cell more frequently and more generally than is the case with others. These changes, which usually make their appearance about the 8th day (and sometimes earlier) continue throughout the illness, and in the more severe cases there are grounds for believing that the polymorpho-nuclear cells suffer extensive disintegrative and destructive changes in the blood itself.

The interpretation to be placed on these facts is no doubt difficult, but they would appear to justify the conclusion that a positive chemiotaxis of moderate degree is exhibited by this cell towards the toxines of Variola, resulting however in its partial destruction. Having regard not merely to its destruction in the blood, but to its migration and destruction in the skin itself, with themaintenance of an absolute increase, the extent to which the bone-marrow is drained not only of transitional forms but of neutrophile myelocytes (See Section3) becomes an easily intelligible fact.

LYMPHOCYTES and SMALLER HYALINE CELLS.

It is the marked increase in cells of this class which

confers on the leucocytosis of Variola its specific characters. Their increase, which is both a relative and absolute one, occurs at the expense almost entirely of the polymorpho-nuclear variety, and the figures representing them, both relatively and absolutely, may almost be regarded as complementary to those of the preceding type of cell. Their proportion is accordingly highest between the 8th and 10th days of the disease. Their average proportion at this date in cases of the first group amounts to nearly 50%, but sometimes they constitute (Cases No.1 and 7) no less than 61.5 to 66% of all leucocytes present. Their absolute numbers therefore in the milder cases frequently approximate to that of the polymorpho-nuclear cells on the 8th or 9th day and in exceptional cases exceed this number.

In more severe cases, however, the relative proportion though still high, does not attain the level observed in the cases of Group 1, and the greatest relative increase is recorded at a somewhat later stage in the illness (about the 13th day on an average).

In the most severe class of cases, the relative and absolute increase of this variety of leucocyte, although present as in the others, is to some extent masked by the appearance in the blood, of myelocytes in greater

or less numbers - an occurrence which also accentuates the polymorpho-nuclear reduction. The increase in the varieties of cells at present under discussion continues in complementary fashion to the polymorpho-nuclear decrease till a tolerable late period of the illness.

Both the lymphocytes and the smaller hyaline cells enumerated along with them present evidences of degeneration but not to the same extent as the polymorpho-nuclear cells.

LARGE HYALINE CELLS.

The data supplied by my observations differ somewhat according to the case, In the milder cases, the proportion of these cells in the blood exhibits fluctuations which vary directly with those of the previous category. Sometimes in these cases, however, a gradual and slight relative fall has been noted. In the more severe cases these cells show an increase both relative and absolute. This rise in numbers appears generally to coincide with the increase in the Smaller hyaline variety and therefore makes its appearance about the 9th day of the disease, after which period its proportions decline. The greatest relative increase is represented by 7 or 8%.

EOSINOPHILE CELLS.

These cells as a rule are increased both relatively and absolutely in the earlier stages of the illness, but undergo a distinct reduction in its later period. In some of the severer cases (Nos.11,12 and 14) an increase in these cells only makes its appearance shortly before the termination of the case.

Eosinophiles of the mononuclear variety are only very exceptionally seen, and always in the most severe forms of the disease. Degenerative changes are not seen in these cells as frequently or to the same extent as in the other varieties.

MYELOCYTES (Mononuclear Neutrophiles).

The appearance of the mononuclear neutrophile in the blood is a very general one in Variola, but the proportions constituted by it vary very much according to the severity of the case.

In the cases of Group 1 for instance, myelocytes were altogether absent from the blood or were met with only in isolated instances. They made their appearance in such cases between the 7th and 12th days of the disease, and were absent from the blood altogether at both an earlier or later period.

In case No.5 however, which, as regards its degree of severity, approached those of the second Group, the maximum proportion of Myelocytes present amounted to 3.5% of all white cells, and in this case they averaged 1-2%. In mild cases of Smallpox modified by vaccination therefore, the Myelocyte, occurring at and after the period of pustulation is met with in very sparse numbers and as a rule does not exceed 1-2%.

In Group 2, the maximum percentage of Myelocytes observed was 6.5% (case No.10). Although the proportion is variable, their occurrence in these cases with abundant discrete eruption is constant.

It is in cases of the greatest severity however, as represented by Group 3, that their relative proportions in the blood attain a very high level. Although their proportions are still very variable in different cases of this class, it may be said that they will generally found to constitute from 10-20% of all white cells present. The exceptionally high figures quoted under this category in case No.12 are partly due(as explained in a note appended to the case) to the inclusion of a large number of "transitional" forms under this title.

NUCLEATED RED CORPUSCLES.

These elements, abnormally present in the blood of the

adult, make their appearance in very variable numbers in the blood in Variola.

In the mildest cases, their occurrence is quite exceptional - they rarely come under observation. They appear in greater numbers, however, in more severe cases and in the blood of haemorrhagic or confluent pustular cases with haemorrhages as many as 17-20 examples may be encountered whilst counting 300 leucocytes. As a rule, the nucleated red corpuscles seen are of the smaller normoblastic type, but megaloblasts also occur in the most grave cases and not infrequently such cells possess either an intensely stained lobulated nucleus or two or more completely separate nuclear masses. (See Fig 3.).

In general it may be said that these cells make their appearamce in the blood at the same time and under the same conditions as the myelocyte and have appeared to me to vary directly with the proportions of this latter type of cell.

I have therefore come to regard the presence of the nucleated red corpuscles in the blood in Variola as an accidental occurrence and due to its being swept into the blood stream along with the myelocytes which are leaving the marrow in much larger numbers.

The conclusions which my observations on the blood in Variola enable me to make may now be summed up as follows:-

(1) Variola in all its manifestations, is accompanied by leucocytosis. This reaches its maximum on or about the 9th day of the disease after which it slowly wanes or may later undergo an increase due to complications. It is most notable in cases undergoing marked and generalised pustulation and although of moderate degree, is still present in transient fashion in the most severe cases.

(2) The characteristic feature of variolar leucocytosis is the relative and absolute increase of the smaller hyaline cells and lymphocytes with which it is accompanied - a condition associated regularly with a relative reduction of the polymorpho-nuclear elements, though these, absolutely, are augmented.

This characteristic leucocytosis is maintained for a considerable time after the acute stage of the illness has passed.

(3) It is characterised also by the presence in the blood of elements normally occurring in the bone-marrow in numbers which are not realised in other acute infectious diseases. These include, besides the mononuclear neutrophile, neutrophiles of transitional type,

mononuclear eosinophiles, large hyaline cells and nucleated red corpuscles of both varieties.

SECTION 2. PART 1.

THE HISTOLOGY of the SKIN in VARIOLA.

Of all the clinical manifestations of Variola, the cutaneous reaction as evidenced by the eruption, is the most remarkable. It may be confidently stated that in the eruption at least the virus certainly exists. Its acme of virulence is apparently reached just prior to the stage of turbidity of the vesicular contents, and diminishes during the period of dessication.

The crusts however retain their infective properties for a period of about two years after removal. What is probably the most ancient method of conferring protection against the worst forms of Smallpox as practised in China and India as early as B.C. 1500, is based on the fact that the variolar virus preserved in the dry crusts from the eruption undergoes a gradual attentuation of its virulence. Such crusts, when dried, powdered and administered as snuff, induced a mild attack of Variola which conferred immunity against the disease.

There are also sufficient grounds for the belief that the disease is essentially a septicaemia and that the eruption is directly related to the transit of the virus from the blood to the whole cutaneous surface. It seems rational therefore to regard the eruption as a

means of defence - possibly one of the means by which the virus is eliminated. It follows of necessity that the character and amount of the eruption may be taken as a gauge of the severity of the case - a conclusion fully warranted by clinical experience.

Further, the occurrence of such remarkable and, for an infectious disease, of such exceptional changes in the characters of the leucocytes in the blood from an early period of the illness, affords the best ground for the anticipation that, the arrival of the virus in the skin will be attended by changes closely comparable from a qualitative point of view with those already in existence in the blood.

The study of the histology of the variolar eruption and especially of the cellular constituents of the eruption, therefore, derives interest from a new point of view. In the following statement of my observations, emphasis will accordingly be laid on the characters of the cells, more particularly of the leucocytes found in the eruption. (See Part 2 of this Section).

As might be anticipated, I have confined myself to the histological phenomena of the eruption from its commencement to maturation; the subsequent stage of healing of the lesion has not been so minutely studied,

although it has come under observation also.

METHODS. The portions of skin selected were as a rule taken from the abdomen, thigh or dorsum of foot. These were fixed at once in one or other of the following fluids

(a) Saturated Solution of Corrosive Sublimate in 1% NaCl solution.

(b) Absolute Alcohol.

(c) Picro-Corrosive-Formal:-

Sat. Sol. Corrosive Sublim. in 1% NaCl sol.	25.
Formal.	10.
Picric acid.	1.
Water to	100.

(d) Muller's fluid 95.)
Glacial acetic acid 5.)100.

They were then embedded in Paraffine, toluol being selected as the best intermediate reagent after dehydration.

The earliest visible lesion consists in a series of irregular minute dilatations of the lymphatic spaces immediately below and sometimes extending between the deepest cells of the Malpighian layer. These spaces are either empty or contain a small quantity of finely granular material, probably the result of coagulation by the fixative and other reagents employed. This is the more likely from the fact that such material is deposited

round the margins of the small spaces referred to. Besides this finely granular material, one observes occasionally larger bodies (about twice the size of a single coccus) which stain faintly by the nuclear dye employed. Although of the same size and form, their faint "nuclear" staining offers a marked contrast to the intense colouration of other bodies, mentioned later, especially in connection with haemorrhagic cases. It is noteworthy however that certain minute bodies are occasionally present at a stage considerably antecedent to that at which any nuclear fragmentation is visible.

From a very early stage therefore, the superficial layers of the hypodermis and the basal cells of the Epidermis are saturated with lymph. In a situation corresponding with the state of matters just described, there is generally to be observed a small area in the mesial prickle zone of the epidermis in which the cells are more faintly stained than other cells of the same zone in the neighbourhood. In this area, involving perhaps 6 - 10 cells, nuclear staining, though reduced in degree, is still present, and Weigert's view therefore that the initial lesion is of the nature of a necrosis appears incorrect. The protoplasm of these cells, which

are somewhat swollen, is finely granular and contains one or more vacuoles. These, as they increase in numbers, coalesce, so that finally the nucleus of the cell is united to the cell-membrane only by delicate bridges of protoplasm. The cells so affected present a reticulated appearance and are clear and swollen - a condition to which Unna has applied the term "reticular colliquation".

Laterally to this area many of the cells show perinuclear vacuoles of varying size, similar to but smaller than those described below in the Malpighian layer. (See high power drawing. Fig. No. 5.)

Beneath this area, the cells of the Malpighian layer are in some instances swollen, in others evidently compressed. In addition, they are to some extent separated from each other. This dissociation of the cells of the Malpighian layer, and the reticular degeneration of the cells of the mesial zone above described involves in each case the loss of "prickle" processes. These however, are clearly visible between the cells in the immediate vicinity of the developing element.

Certain of the cells of the Malpighian layer undergo considerable increase in size. In many, a vesicle appears which enlarges gradually until the cell is

"ballooned" out into a clear sac, the nucleus being applied crescent-fashion to some part of the exterior, while the protoplasm of the cell forms the thinnest possible rind. It is in this zone that the "ballooning colliquation" referred to by Unna occurs in Variola.

Other cells however of this layer are evidently from the first subjected to pressure. This is apparently the result, on the one hand, of the presence of the swollen cells referred to, and on the other, of the irregular saturation of the cutis with lymph. The naturally elongated form of these cells becomes exaggerated, both nucleus and cytoplasm showing the evidences of compression. Their protoplasm at the same time becomes cloudy and stains more deeply than normal by acid dyes; nuclear staining, however, in these as well as in the swollen cells is preserved.

Unna maintains that both the "reticulating" and "ballooning" forms of epithelial degeneration are fibrinoid, inasmuch as the granular matter of the delicate intra-cellular strands in the former case, and the marginal zone of protoplasm in the latter, respond to staining methods for fibrine. The application of different modifications of Weigert's fibrine method has not, in my hands, confirmed this point.

The condition of matters in the Malpighian layer may therefore be summarised by saying that the inter-cellular lymph spaces are widened from below upwards, involving the loss by rupture of "prickle" processes, and that of the cells, some are elongated and compressed, while others enlarge and ultimately rupture, from cellular oedema.

Superficially, at this stage the eleidin layer is increased, consisting of three or four cells in depth. These are swollen out in oval, or almost circular fashion with their characteristic granules arranged round the periphery of an enlarged perinuclear space.

The minute cavity of the commencing vesicle originates by rupture of the membranes of cells which have undergone the reticular changes described as occurring in the cellsof the mesial prickle zone, and the communication therefore of several cavities of intra-cellular origin. The cavity of the developing vesicle is in communication with the distended lymph spaces of the hypoderm by a series of dilated inter-cellular channels traversing and opening up the Malpighian layer, as already described. By distension with lymph the cavity thus formed increases steadily in size. Its further increase is brought about by a succession of similar

changes occurring in the cells bordering the primary cavity on its superficial and lateral aspects.(See Fig6)

The swollen eleiden layer is thus encroached on by thevesicle from beneath, and over the apex of the vesicle the cells of this layer may be observed to be flattened out and compressed. Immediately beyond the summit of the vesicle, however, in a lateral direction the swollen cells of the eleidin layer again become manifest, and as the cells of the mesial prickle zone in this situation are also swollen, the developing element has at this stage the macroscopic appearance of a bluntly pointed papule. It is the case therefore, as Buri has pointed out, that what is macroscopically a solid papule is already, histologically, a small vesicle.

By further encroachment from beneath on the eleidin and corneous layers, and their consequent thining, the small vesicle becomes apparent - the clear fluid contents of the cavity being rendered visible through the thin stratum corneosum and constituting the now translucent apex of the papule. Not infrequently, at this stage, the eleidin layer has ceased to be demonstrable over the summit of the developing vesicle. In the cases of many of the pocks, however, the eleidin

layer persists until comparatively late - till near the attainment of the acme of the element at least.

The effects of the initial lesions in the Malpighian layer are, at least in the benign elements at present being described, soon accompanied by regenerative changes in the cells of this zone situated immediately beyond the centre of the base of the pock. In this situation the process of a-mitotic nuclear division may be frequently observed; the occurrence of mitotic figures is more rarely met with. This proliferative activity in the Malpighian layer in the immediate vicinity of the vesicle plays an important part in the later stages of the eruption.

The contents of the cavity as thus described, consist of clear lymph, containing very few cellular elements. These are almost exclusively comprised of lymphocytes which may be fairly numerous in the lymph spaces of the hypoderm immediately beneath the Malpighian layer.

Polymorpho-nuclear cells are very infrequently present in the early stage. A survey of the contents of the blood vessels in the superficial layers of the hypoderm also shows the small mononuclear cells to be the most numerous, polymorpho-nuclear cells being very rare.

These facts are perfectly analogous with what occurs in Vaccinia (Buri 1892: Mann, 1899) and Varicella at a similar stage.

With the gradual increase in size of the cavity of the vesicle, its fluid contents become more rich in cells, and consequently turbid. It has been and still is, customary to apply the terms "pustular" and "suppurative" to this stage of the variolar eruption whose elements have now, macroscopically assumed the appearance of small, more or less prominent, flattened hemispheres of opaque gray or more frankly yellow colour.

From the statement of the results obtained by examination of cover glass film preparations of the contents of the eruption at various stages, the cellular, often highly cellular characters of the contents is a matter which admits of no doubt. That the pustular character of the eruption however is primarily or even mainly due to the presence of leucocytes of the polymorpho-nuclear variety, I am not prepared to admit. The latter cells have never appeared to me to constitute more than 50% of the total numbers and frequently the proportion constituted by them is much less.

The contents of the mature turbid vesicles so far as the leucocytes are concerned, are composed mainly

of hyaline cells, especially of the smaller class, and polymorpho-nuclear cells, the former being as a rule more numerous than the latter. In no case however, can the turbid material of the "pustule" be regarded as "pus" in the sense that polymorpho-nuclear leucocytes almost exclusively comprise its cellular elements. Even in instances where the eruption is invaded by pyogenic cocci no such accession of polymorpho-nuclear cells follows as would, under other circumstances, inevitably occur.

It is interesting to note in this connection that suppurations, occurring on a larger scale during Variola are also characterised by the relative abundance of the smaller hyaline cells.

The specific leucocytosis in the blood in Variola appears therefore reproduced in the skin and in suppurative processes supervening during the disease.

A fact of this kind affords the best possible basis for the belief that the leucocyte emigration which occurs in the variolar eruption in character as well as in amount, is one of the essential phenomena of the disease.

From the few observations which have as yet been made on the blood and cellular elements of the skin in Varicella, a similar state of matters seems to be

established in that disease, the inference therefore being permitted that the causative agent in both, is closely allied.

Apart from the character of the leucocytes however which make their way into the cavity of the vesicle the amount or degree of leucocyte emigration is in many instances insufficient in itself to explain the viscid puriform appearance of the "pustular" contents.(Fig. 8)

On this point I find myself in disagreement with Unna who, speaking of the eruption from the 5th day onwards says:- "A full stream of leucocytes, no doubt attracted by the germs lying dead in the tissue runs through the whole cutis and reaches in the papillary body such a density that even in thin sections, the margin between cutis and prickle layer is hardly recognisable. This goes on untill the whole cavity is densely infiltrated with white corpuscles etc".

I have not met with such appearances - at least in typically developing and discrete elements. It may be partially true of the atypical characters of certain intra-epidermal abscesses in the "badly developed" eruptions of confluent or semi-confluent cases.

The progressive degeneration and dissolution of epithelial cells however may be a prominent feature in a

cavity whose leucocyte contents are not abundant, and as a factor in producing the peculiar material of the "pustules" has, I believe, not been sufficiently emphasized.

The cavity of the mature vesicle as thus described is by no means a simple sac. Neither is it, as is so frequently stated, multilocular. It is in the great majority of instances essentially a unilocular cavity traversed by incomplete dissepiments of varying degrees of thickness. Of these, only a small proportion traverse the cavity from floor to roof, and, even when this is the case, they do not extend throughout the whole diameter of the vesicle.

The septa, both of the finer and larger varieties although epithelial in origin, arise in a different manner. The majority of the latter arise from the greatly elongated cells, or strands of two or more such cells previously described as originating in the deeper parts of the prickle layer. These, which at first scarcely penetrate the base of the vesicle come to project more and more into its cavity during the later stages of its development. This result is apparently brought about by the proliferative changes alluded to as present in the neighbouring cells of this zone, by which the compressed cells are thrust upwards into the

cavity of the vesicle.

Occasional septa, more bulky than the preceding are also seen, evidently composed of strands of altered epithelial cells, the nuclei of which still retain in some degree their affinity for nuclear dyes. These cords (as seen in section) of epithelial cells represent strands of the mesial prickle layer which, having escaped the reticular colliquation of Unna from the first, persist, at least for a time, as bridges spanning the cavity.

(The septa of the kind above described are really laminar in form, as is seen when their plane happens to correspond with that of the section, and it would consequently be more correct to conceive of them as incomplete curtains of cells traversing the cavity, not always in parallel directions).

The finest septa, often visible only as delicate lines with some finely granular material deposited on them, represent portions of the persistent mantles of single cells of the mesial prickle layer whose contents, after colliquation and partial rupture of the cell-membrane, have been poured into the cavity of the vesicle. (See Fig. 7).

It is not without interest to myself to discover that my observations on the mode of formation

of the septa in the variolar vesicle are in almost complete accord with those of Balzer and Dubreuilh whose conclusions (Dictionnaire de Medecine - Art. "Variole" by Barth and Vilocq p.476) only came under my notice some time after the foregoing was written.

Umbilication, as a very general feature of the variolar eruption is one which is constantly described and must be here briefly referred to. It may be observed in the developing vesicle at an early stage (2nd to 4th days of the eruption, according to the site) it disappears during the maturation of the vesicle, and re-appears generally in more marked fashion, during its recession. It is customary therefore to speak of "early" and "late" umbilication in Variola.

I may remark at the outset that umbilication, although very general, is by no means a constant feature of all the elements of any variolar eruption. It often exhibits considerable variations in degree, and in some cases is almost altogether absent.

The phenomenon of umbilication, when it appears in a young developing element, is brought about by two or more causes, acting in conjunction. One of these depends on the fact that the cells of the mesial prickle zone surrounding the vesicle are, from oedema and

reticular colliquation, greatly increased in size. The other principal factor contributing to the result is the proliferative activity of the cells of the Malpighian layer in the lateral environment of the vesicle. From these two causes, the peripheral portion of the increasing vesicle occupies a relatively higher position than the central part; it is in fact, raised above the level of the surrounding skin surface, while the position of the central portion is little affected.

Another manifest cause of umbilication is the coincidence of the site of the vesicle with the presence of a hair-follicle. The deeper cells of the follicular sheath in such a case do not share to anything like the same extent in the changes which are proceeding in their neighbourhood, the thin cornified layer of the neck of the hair follicle offreing a barrier to the process. In this way, the periphery of the vesicle is ballooned out round the follicle which of course constitutes the depressed centre. Unna refers to this as quite an accidental and exceptional cause of umbilication in Variola. From my observations both of the naturally occurring eruption and of microscopical sections of the same, I believe that it is by no means an uncommon occurrence.

The re-appearance of umbilication during the

receding stages of the eruption is caused by the absorption of the more fluid contents of the pustule by the neighbouring lymphatics and the consequent collapse of the central portion of the roof of the vesicle.

Already at this stage there are indications of the healing process. The proliferative activity of the cells of the Malpighian layer has caused the cavity of the pustule to assume a relatively superficial position. Its base becomes more sharply differentiated from the thick and cellular cushion on which it rests by the appearance of corneous changes in the upper cells of this layer, which from this stage onwards is being actively added to from beneath. (See fig. 12).

This zone of cornified epithelium, delicate at first, extends from the periphery of the pock inwards, very much (as Unna has described it) after the fashion of a gradually closing iris diaphragm until the pustule is completely separated by it from the active epithelium beneath.

From the time when the pustule has in this manner been practically excluded from the actively regenerating epithelium, the process of healing as a rule proceeds uninterruptedly. If however, before the newly forming corneous layer has become continuous under the

base of the pustule, rupture of the element with possibly secondary microbic infection occur, the healing process only occurs after further destruction of the regenerating layers, with more permanent scar-formation.

CONFLUENT and HAEMORRHAGIC CASES.

Although the series of changes above described are also present in the most severe forms of the eruption, their regular sequence cannot be traced as a rule, in such cases. It may be stated generally that in confluent cases, the initial lesions by which the Malpighian layer is opened up and its cells separated and distorted or swollen and degenerated are present over considerable areas of the skin. The cells of the mesial prickle layer also only escape the changes peculiar to them in small islands so that from an early stage disintegration of the Malpighian layer with irregular, sometimes almost continuous, vesicle-formation in the prickle layers, are visible throughout entire sections of the portions selected for examination. In these cases, the corium, whose collagenous bundles are swollen and degenerated is, from an early period, infiltrated with blood corpuscles as well as leucocytes almost exclusively of the non-granular mononuclear variety. Both cells readily invade the skin, their entrance being aided by the changes in it above described. The red

corpuscles especially make their way through the skin, insinuating themselves between the cellular laminae of the superficial scarf skin. (See FIG. 13.)

It is in such cases that, small intra-epidermic abscesses are apt to arise. These which occur irregularly, and are filled with leucocyte, nuclear and other debris, rapidly form after disintegration of the Malpighian layer, and are not comparable either in mode of origin or appearance with the typical pustule of Variola.

In haemorrhagic cases, in addition to the changes above mentioned, the infiltration of the upper layers of the hypoderm by haemorrhages is a characteristic feature. These frequently extend along the hypoderm, in scattered fashion, for considerable distances, and penetrate between the connective tissue bundles to some depth.

In speaking of haemorrhagic cases, it must be stated that the use of the term is confined to cases in which blood is extravasated in some quantity into the connective tissue of the corium as now described. The presence of red corpuscles in the cavity of the Vesicle at various stages may be determined in many cases of tolerably mild character, an escape by diapedesis of this kind having no relation, clinically or histologically, with the severe cases in which the larger haemorrhages

above alluded to, occur.

The connective tissue bundles not only at, but for some distance round the site of such a haemorrhage are swollen and degenerated, taking on a diffuse, indefinite protoplasmic staining. (See Fig. 14).

In connection with these haemorrhages special mention must be made of multitudes of small bodies staining very deeply with nuclear dyes which are present among the red corpuscles. These are frequently present in such numbers and so definitely removed from any area of nuclear fragmentation as to render this explanation of their origin, in my opinion, inadequate. The fact also that from such situations, numbers of these "bodies" may be perceived streaming upwards into the epithelium, appears to favour the assumption that they are possessed of some amoeboid activity. (See Figs. 14 & 15).

While unwilling to make any statement as to their possible parasitic nature, I am not, on the other hand, at all convinced of the fact that they are entirely of cellular or nuclear origin.

SECTION 2. PART 2.

THE CONTENTS of the VESICLES and PUSTULES in VARIOLA.

According to the purpose which different investigators have had in view, the cutaneous variolar eruption has been in different ways the subject of examination.

Numerous investigations, based on the conclusion to which all evidence leads viz. that the parasite of Variola is surely present in the skin during the greater if not the entire period of the eruptive manifestations of the Disease, have been concerned with the search for the specific cause.

These researches have been pursued along two lines of enquiry. On the one hand, careful bacteriologi cal examinations of the eruption have been made with the view of finding a specific organism biologically related to the lower bacteria as the cause of the disease, and on the other hand, believing the parasite of Variola to be a species of protozoon, other enquirers have adopted particular methods.

During the earlier period of my research, I examined cover glass film preparations from the variolar vesicles or pustules of 36 cases. These included the preparation of films from the eruption at varying

intervals in each case, and in addition similar investigations were carried out in the cases reported on in the first section of this work. I have thus examined in all 54 cases from this point of view. These investigations have caused the following questions to possess for me a considerable interest viz.

(1) The relation of micro-organisms to Variola and especially to its cutaneous manifestations.

(2) The relationship of Protozoa to Variola.

(3) The cellular and particularly the leucocytic and leucocyte-forming constituents of the contents of the eruption, and the relationship between these and the condition of the blood.

(1) THE PART PLAYED by ORGANISMS in VARIOLA.

Until within comparatively recent years, textbooks both in Medicine and Pathology have been in almost complete agreement in making the statement that the suppuration observed in the Variolar eruption from about the 9th day of the disease onwards is always attributable to the presence of pyogenic microbes. Bacteriological researches however rendered the considerable modification of this statement necessary.

In 1886 and 1887, Guttman published the results of his examinations of the eruption. From several cases

investigated he isolated in culture and identified the following micro-organisms:-

Staphylococcus Pyogenes Aureus.

do. do. Albus.

do. Citreus.

do. Viridis flavescens (which had been previously described in the eruption of Varicella).

Staphylococcus Epidermidis Albus (although not named, Guttman's description of a non-pathogenic white coloured micrococcus apparently applied to this organism).

Streptococcus Pyogenes.

Pneumococcus.

Guttman, while he recognised the fact on the one hand that the turbid fluid from the pustules in Variola is not pus in the ordinary sense, and on the other, that many elements of the eruption undergoing the same series of changes are free from organisms, concluded nevertheless that the suppuration which occurs in Smallpox is directly connected with the presence of pyogenic cocci.

It is not therefore a matter of surprise that Pick (1892) concluded that suppuration was not an essential feature of Smallpox - a conclusion which we have seen led him to deny in Smallpox strictly so called, the existence of leucocytosis.

Later investigations however have shown that although the presence of micro-organisms is a frequent feature, it is by no means constant, and further, that it may be very accidental in nature. Thus, although examination on a particular day has failed to reveal any organisms, their presence in large numbers may be demonstrated the next day in elements in the immediate vicinity of those previously examined. Further, I am able to state that if a considerable number of pustules over a limb be examined, an insignificant number only will be found to contain organisms. Pyogenic cocci are much more frequent in pustules in situations which lead to their rupture. The organisms are almost never in the interior of cells - always free.

It may be here stated that the presence of pyogenic organisms does not produce any decided alteration in the characters of the leucocytic constituents of the eruption, and in particular, it does not lead to any marked increase in the polymorpho-nuclear leucocytes.

These organisms, as it appears to me, after a more or less accidental invasion of the eruption, multiply locally without producing any marked tissue reaction whatever. As figured (See Figs. 17, 18) they become applied to the roof, sides and persistent epithelial cords

spanning the cavity of the pustule, and only exceptionally are found in the corium in close relationship with either blood or lymph vessels. It is interesting in this connection to notice that in some severe cases in which such organisms have been found in the eruption during life, I have noted their presence in the bone-marrow and spleen after death. In these tissues moreover, as in the skin, the organisms lie in dense clusters without having apparently induced any inflammatory reaction.

From facts such as these, I am led in accordance with Weil (Etude leucocytaire de la pustule varioloque) to conclude:-

(1) That the leucocyte emigration which occurs in the variolar eruption, both as regards its nature and amount, is an essential phase of the disease process and that it is neither due to, nor materially modified by, the presence of pyogenic organisms.

(2) That these when present, are the result of accidental invasion, not always simultaneously, of different limited portions of the eruption, and that their role in the phenomena in the skin, is quite subordinate to those already in existence, associated with the disease itself.

(3) That the association of pyogenic organisms in the skin during life with their presence in certain tissues

and organs post-mortem is probably to be explained by their invasion of the blood shortly before death, in cases in which the fatal issue is directly due to Variola itself.

Although the presence of bacilli may be occasionally determined in the Variolar eruption, they are not common.

My researches do not permit of my making any statement with reference to the bacillus described by Klein and Copeman, which necessitates special staining methods, and I have been concerned rather with the relations of pyogenic organisms to the disease, and particularly to the specific leucocytosis of Variola.

(2) PROTOZOA in VARIOLA.

Since the announcement by L.Pfeiffer and Van der Laeff (in 1886) that "numerous small bodies, capable of independent amoeboid movement" could be demonstrated in the lymph both of Vaccinia and Variola, considerable interest has attached itself to their presence and nature. Such bodies were designated by Pfeiffer "Monocystis Epithelialis".

Guarnieri (1892) regularly found in the pre-pustular stage of Variola minute bodies which sometimes attained the approximate size of half the nucleus of an

epithelial cell, but were as a rule, much smaller. These, which occupied the protoplasm of the cells in the area affected by the eruption, stained uniformly and regularly. Although assuming various forms, they were most often rounded with slightly irregular margins. He obtained "bodies" similar in all respects to the fore going in the deeper cells of the rabbit's cornea which had been scarified with either vaccine or variolous lymph. They were composed, according to Guarnieri, of a minute oval nucleus and a marginal protoplasm which assumed very varied forms from amoeboid activity. These bodies were named by him Cytoryctes Variolae seu Vacciniae.

Several observers (Unna, Ferroni and Massari etc.) however believed that such experiences might be explained by nuclear or leucocyte derivatives, and further that they were not specific to Variola, but could be produced by the action of such substances as Croton oil, indigo etc. Working in the same year (1892) as Guarnieri, Doehle found in the blood of patients suffering from Variola, and also in those suffering from Measles, Scarlet fever and Syphilis, bodies similar in all characters to those described by Guarnieri. The presence of similar bodies in the vesicles and pustules

of Variola was also confirmed by the same author, who further stated that their motility was due to a flagellum of considerable length.

In 1894, Pfeiffer confirmed Guarnieri's results and also announced the presence of the parasite in the blood of smallpox patients and in that of vaccinated children and calves during the febrile period. Pfeiffer considered that Guarnieri's bodies as well as those described in the blood were the younger stages of the parasite to which, in the form of a clear body containing numerous spores he had applied the term Monocystis Epithelialis.

Since that time observations on the blood and lymph in Variola and Vaccinia have been multiplied (Weber, Reed, Hückel etc.) the general results being in agreement as regards the presence of minute, more or less actively amoeboid bodies in these conditions.

The interesting researches of MM. Roger and Weil (1900) must now be briefly referred to in this survey of the subject. These authors, besides noticing the presence in variolous lymph and in theblood of minute, apparently nucleated amoeboid bodies had the opportunity of examining Amniotic fluid from two cases of Variola. In this fluid, which was free from leucocytes and contained

only a few epithelial cells, these bodies were strikingly numerous, and their amoeboid movements were unusually active.

They further succeeded in obtaining cultures of these bodies by incubation of an excised portion of the carotid artery of a rabbit which had been inoculated with variolar pus, the blood after 48 hours incubation containing them in considerably increased numbers.

Further, they showed that such cultures possess a pathogenic action on rabbits, producing a septicaemia occasionally with the development of a few pustules,- a condition similar to if not identical with that produced by direct inoculation of the contents of variolar pustules.

My own observations on the contents of the variolar eruption at various stages lead me to say that there undoubtedly occur, in greater or less numbers, minute, either oval or rounded structures, possessing a nucleus which stains very deeply and definitely with nuclear dyes surrounded by a narrow and sometimes irregular marginal zone of protoplasm. These bodies vary in size from the dimensions of a coccus (Staphylococcus) to about a quarter the diameter of a red blood corpuscle. I am convinced, however, that they cannot be with accuracy

differentiated amidst the varied and sometimes not dissimilar results of cell-degeneration and fragmentation so abundantly present in the contents of the eruption in its later stages. Bodies such as these however are certainly demonstrable in microscopical sections under such circumstances (absence of cell-degeneration in early stages etc) and in certain cases in such numbers, as to attach to their presence an undoubted significance. These have been already mentioned in the description of the histological changes in the skin. (See previous part of this section). (See also Figs. 14, 16 & 19).

(3) CELLULAR CONTENTS of the ERUPTION.

These were studied in films fixed in the following ways:-

(1) Fixed wet in Saturated Mercuric chloride solution.

(2) In Formalin and Absolute Alcohol.

(3) By Heat.

The staining methods employed were Haemalum and Eosine, Ehrlich's acid Haematosylin with Eosine and Orange Carvol Thionin blue with and without Eosine, Gram's method and in the case of films fixed by the two last processes Ehrlich's triacid fluid.

The following is a summary of the principal facts noted, in connection with each cellular constituent.

(1) POLYMORPHO-NUCLEAR NEUTROPHILE CELLS.

These are present in cases of all degrees of severity.

They occur somewhat sparsely in the clear fluid obtained from early vesicles (6th day of illness) but from this date onwards they occur in increasing numbers. They are probably most numerous from the 10th to 12th days of the disease, after which they steadily decline. The thin puriform fluid which may be obtained from some pustules as late as the 17th or 18th days of the disease contains very few of these cells in advanced state of degeneration. At any stage of the eruption, only a minority of these cells will be found free from degenerative changes. The appearances produced by such changes are very varied. Probably the most common is that in which the nucleus breaks up into from 4 to 12 small spherical masses of every variation in size. These, which stain very deeply occupy as a rule, a peripheral position, and have the appearances depicted in Figs. 20 & 21.

If as a result of further investigation, such degeneration nuclear masses become free, or associated with a thin protoplasmic envelope derived from the original cell (Fig.) The similarity in appearance between the parasitic bodies above described and such products becomes at once apparent The proportion of polymorpho-nuclear cells to all other forms present is from 40% to 60%.

(2) LYMPHOCYTES and SMALLER HYALINE CELLS.

These are present during the whole of the eruptive stage and reach their acme about the same time as the cells of the foregoing type. They have appeared to be almost if not quite as numerous as the above, but do not disappear from the pustular contents so quickly. It is the relative abundance of this type of cell which aids in conferring on the puriform contents of the variolar eruption its specific character.

(3) LARGE HYALINE CELLS.

These are present in quite insignificant numbers. It is difficult to classify these cells in the contentc of the eruption, as appearances more or less resembling them are produced in altered epithelial cells etc. They are frequently so altered themselves by degenerative changes that their recognition is a matter of difficulty.

(4) EOSINOPHILES.

The polymorpho-nuclear variety is as a rule fairly frequently met with in the earlier stages. Relatively speaking, they are sometimes quite numerous, but their frequency only becomes a striking feature in exceptional instances. As a rule, they undergo disintegration readily, so that free eosinophilous granules or fragments of these cells are more often seen than complete examples.

The occasional presence of mononuclear eosinophiles in the eruptive contents of the more severe cases is a noteworthy feature.

(5) MONONUCLEAR NEUTROPHILES.

These have been observed very occasionally in the eruptive contents of cases resembling those of Group 2. In the most severe cases however, they may be a little more numerous. In no case, however, are they at all readily found, and I hesitate to accept the statement of Weil (Etude leucocytaire de la pustule varioloque) that they not infrequently constitute 10 - 20% of the total cellular constituents.

(6) RED CORPUSCLES.

These are present in tolerably mild cases in small numbers fairly frequently. In such cases as those represented by Group 2 of previous section, few of the elements examined will be found free of them, though the eruption in its naked eye features conveys no suggestion of their presence. In the most severe cases, and especially in haemorrhagic forms, the presence of nucleated red corpuscles can usually be demonstrated.

Other cellular constituents are composed of swollen and otherwise altered epithelial cells, and, more occasionally of multi-nucleated cells. The latter,

which sometimes attain a large size, have lobulated or scattered nuclei and sometimes contain lymphocytes or red corpuscles in their interior.

It will be thus seen that the leucocytosis of Variola is reproduced in a closely comparable form in that present in the eruption. If we are correct in viewing the variolar eruption as the result of an intense local reaction perhaps occasioned by the escape of the parasite from the blood, a possible reason appears for the similarity of the cells which make their way to the continuance of the struggle against the virus in the skin and those whose marked increase in the blood has been induced and maintained by its presence there.

THE BONE-MARROW in VARIOLA.

SECTION 3.

The character of the leucocytosis in Variola is such that a study of the haematopoietic organs is necessarily fraught with interest. The notable increase both relatively and absolutely in the blood of especially the small and medium sized cells of the hyaline variety, indicates a related activity of the lymphatic glands and spleen, but also of the bone-marrow; while the moderate but constant absolute increase of the polymorpho-nuclear neutrophiles and the appearance in the blood of mono-nuclear cells of both neutrophile and eosinophile varieties, as well as the nucleated red corpuscles, supply evidence of the extent to which the bone-marrow in particular participates in the tissue-reactions in Variola.

The bone-marrow in Smallpox appears to have been first studied by Golgi in 1873, who examined this tissue in 25 haemorrhagic cases, and 10 suppurative cases of the disease. Anything like a cellular analysis of the contents of the marrow was at that time impossible, and his investigation is not possessed of the interest which attaches to the study of this tissue by modern methods in the light of our more definite knowledge with regard to its relation to the corpuscular elements in the blood.

Golgi however concluded that in the two varieties of cases the marrow presented different characters. In "suppurative" cases, he found the marrow abundant, grey or greyish red in colour and tolerably firm (pultaceous) in consistence. Microscopically this was found to correspond with a tissue rich in leucocytes, and giant cells multiplying by budding - a condition of matters, indicative of an increased activity of the marrow.

In haemorrhagic Variola on the other hand, the marrow was red and fluid, corresponding microscopically with abundance of red corpuscles and relative scantiness of leucocytes or cells.

The relation of these different types of the bone-marrow however to certain types of the disease is not by any means constant, and differences of the kind noted by Golgi are probably not so closely related to the severity of the disease as to the period at which death occurs.

Prof. Chiari in 1893 described as existing in the bone-marrow of smallpox, certain small "necrotic foci". These he characterised as small greyish specks surrounded by a marked inflammatory zone. They occurred especially in the marrow of the long bones (Femur and Tibia were examined) but were not found in the marrow of

flat spongy bones. Believing them to be specially related to Smallpox the expression "Osteomyelitis Variolosa" is used by the author in describing the condition.

In 14 cases examined at the stage of the commencement of the eruption or during the suppurative period, such foci were only found in 7. They were found however in each of 8 cases examined at the stage of dessication. Chiari never found micro-organisms in connection with these foci, which he regarded as comparable both in their macroscopic and microscopic characters with similar multiple lesions in the Testicle in Variola. These lesions in the testicle as well as those in the marrow were regarded by Chiari as the analogue in the internal tissues, of the cutaneous efflorescence, and were in fact termed by him,"internal pocks" as contrasted with "external".

Small greyish specks, sometimes as large as a pin-head, are not infrequent in more especially the diffluent varieties of bone-marrow in Variola. These, however, correspond with cellular collections, in which mone nuclear neutrophiles and hyaline cells abound, and in which active rather than necrotic changes are present.

These earlier investigations however cannot be ranked in importance with those carried out in France during the recent epidemic of Smallpox in Paris and Lyons

MM Roger, Josue and Weil published in August 1900, the results of their examinations of the bone-marrow in 15 cases of Variola. These relate either to confluent or semi-confluent suppurative cases with or without haemorrhage, or to haemorrhagic cases.

The results obtained by them may be summarised as follows:-

(1) The reaction of the bone-marrow varies very much according to the case. Thus in some cases of suppurative Smallpox, the marrow is red and fluid with comparatively scanty leucoblastic elements; in others, these are abundant and show proliferative changes, while sometimes the marrow is yellow and completely fatty with almost complete disappearance of the cells proper to it. Similar differences were observed in the marrow from haemorrhagic cases.

The relation of a special variety of the bone-marrow to suppurative and haemorrhagic cases as stated by Golgi is therefore not confirmed.

(2) The prodomination elements in the marrow are mononuclear cells with and without granules.

(3) When secondary pyogenic infections occur in the course of Variola, a polymorpho-nuclear leucocytosis is not induced.

A similar investigation published by MM Courmont

and Montagard at the same time, yielded somewhat similar results. They also examined 15 cases, and usually selected the marrow from the Sternum, Humerus and Femur in each case. According to the situation examined, the marrow was found to be reddish grey (sternum) or white and friable, (femur). It approximated in appearance and character to that found in the sternum in the upper part of the femur. These authors maintain that the results obtained in each case differ widely according to the situation from which the marrow is taken; in one situation, only some fat and red blood corpuscles will be found, and in another, a great abundance of cells of various kinds. They believe accordingly that if the marrow in Variola be examined in several situations, areas of cellular proliferation will be invariably met with. They enumerate the cellular types met with generally in the marrow and assign to each its relative frequence.

I have had the opportunity of examining the bone-marrow in seven cases of Smallpox. These observations were made both in film-preparations and microscopical sections. The staining reagents employed were; Carbol-Thionin, Eosine and Thionin, and Ehrlich's triacid fluid. The following is a statement of the facts observed:-

Obs.1. Eliz.Mc C. aet 8 yrs. Unvaccinated. Very severe

case with marked pustulation in semi-confluent eruption.

The marrow (from the rib) is red, but fairly firm. Red corpuscles are exceedingly numerous; nucleated red corpuscles are rare. Mononuclear neutrophiles reduced, but still fairly numerous; mononuclear eosinophiles pretty frequently seen. Polymorpho-nuclear neutrophiles are practically absent, though a few transitional forms are seen. Myeloplaxes of large size are not infrequent. Considerable numbers of large non-granular mononuclear cells are seen. In some of these the protoplasm appears to be basophilic after treatment with thionin.

Micro-organisms are numerous and include both Steptococci and Pneumococci. In addition, bacilli joined end to end, and resembling the shorter forms of B Mycoides are seen. It may be added that the two former organisms were found in the spleen from this case.

Obs.2. Jas. M. (See case No.12. section 1. page 77) Rib marrow red and semi-fluid. Red corpuscles exceedingly numerous; nucleated red corpuscles present but not very common - apparently reduced. Of the mononuclear cells, the neutrophiles are reduced, the eosinophiles do not seem to be affected, and thehyaline cells of medium size are numerous. Of the polymorpho-nuclear cells, no examples at all of the neutrophile variety are seen, and only a few

eosinophiles of this class. A few lymphocytes are met with. Myeloplaxes with large deeply stained contorted nuclei are by no means infrequent.

The remainder of the film is composed of free fat globules, disseminated eosinophile granules, and a considerable quantity of granular amorphous matter, with some free nuclear masses.

Obs.3. Alex Mc C. aet 51. Severe case dying during late pustular stage. Semi-confluent.

The marrow is congested, but at the same time highly cellular. Nucleated red corpuscles are pretty numerous; they do not appear reduced. Mononuclear neutrophiles are on the whole reduced, and some show degenerative changes. Hyaline cells of large and medium size are numerous, especially those of thelatter description. Myeloplaxes are fairly common; in some cases these cells contain ochre coloured pigment. This pigment also occurs in granular masses throughout the marrow.

Obs.4. Thos Mc K. (See case No.13. Section 1. page 83.) The marrow is red and diffluent. It consists almost entirely of red corpuscles, the leucoblastic elements being reduced to the smallest numbers. Nucleated red corpuscles are occasionally met with. The other elements present are: large hyaline cells - numerous. Mononuclear

neutrophiles very few. Eosinophiles of either class are very scanty indeed. There is a good deal of amorphous granular matter.

Obs.5. Mc C. aet 55. Haemorrhagic Smallpox.

The marrow is diffluent and of blood red colour, but with some greyish fragments of firmer consistence.

The following description applies to a section stained with the triacid fluid. The red corpuscles are very numerous, mapping out the fat spaces by a dense corpuscular reticulum. The capillaries are distended with red corpuscles. Nucleated red corpuscles are numerous, occurring both free in the marrow and in the capillaries. They are mostly of normoblastic type, but a few megaloblasts are also seen. Mononuclear neutrophiles are only very occasionally seen, and throughout the section are certainly reduced. Feeble or partial staining of thegranules is visible in a considerable proportion of these. Eosinophile cells of both classes are reduced; in many instances these cells have suffered fragmentation and are represented by small collections of eosinophilous granules with a small portion of a nucleus.

Myeloplaxes are infrequent, but sometimes contain in their interior portions of cells or free nuclear

masses. Polymorpho-nuclear cells are very rarely seen. There is a large quantity of amorphous granular matter throughout the section, as well as masses of yellow pigment, both intra-cellular and free. No organisms are found.

Obs.6. Mac. aet 36. Haemorrhagic smallpox, with badly developed eruption. Separate petechiae on face. The facts are somewhat similar to those in Obs.5., but the marrow does not exhibit such complete depletion, the cellular elements being more abundant.

The mononuclear neutrophiles are somewhat reduced, but mitotic figures are occasionally seen in them The nuclei in many contain granules staining a brown colour with the triacid fluid; sometimes these brown granules are of such size as to arrest attention. They may possibly be connected with a condition of nuclear activity. Both varieties of eosinophile cells occurs less frequently than normal. Polymorpho-nuclear cells are distinctly rare. Myeloplaxes are fairly common, as well as free giant nuclear masses. Examples of cellular and nuclear fragmentation occur occasionally. Red corpuscles are everywhere abunfant, and nucleated red corpuscles though easily found, appear diminished in numbers. No organisms are discovered.

Obs.7. P.M. 18/2/01.

Marrow practically fluid with small grains of paler appear ance and firmer consistence.

Microscopically, all the cellular (leucoblastic) elements of the marrow are depleted. Mononuclear neutrophiles in particular are reduced in number. A few cells of the lymphocyte class and smaller hyaline cells are met with. Correspondingly, the red corpuscles are in preponderating excess. Nucleated red corpuscles are not difficult to find, but are certainly reduced. A large quantity of finely granular material present throughout.

The conditions of the bone-marrow in Variola as presented post-mortem are thus seen to differ widely from each other. This tissue is doubtless in a condition of proliferative activity in cases proceeding towards a favourable termination. The appearance, in these cases in the blood, of numerous transitional forms of the polymorpho-nuclear neutrophile, as well as the regular presence during the acute stage, of both mononuclear neutrophiles and nucleated red corpuscles in smaller or larger

numbers shows that the medullary tissue is actively concerned in the maintainence of the supply of neutrophile cells to the blood.

The fact also, that, along with a distinct increase in the leucocytes in the blood, there is regularly an absolute increase in the polymorpho-nuclear cells, although these are relatively diminished, taken in conjunction with the fact that these cells often appear to be undergoing destruction in the blood itself (as well as in the skin) indicates the extent to which the leucoblastic elements of the bone-marrow are implicated during the acute period of the disease.

Speaking generally, the condition of the marrow as seen post-mortem in Variola is one in which this tissue exhibits varying degrees of depletion. In the production and maintainence of the specific leucocytosis of Variola, it reserve supplies are rapidly called upon, and as shown by the observations in Section 1. make their appearance in the blood in smaller or larger proportions. In accordance with the relations of these cellular reserves to the medullary sinuses, the marrow elements come under observation more or less in the following order:-

(Transitional forms of neutrophiles
(and Larger Hyaline cells.

(Mononuclear neutrophiles and
(
(Nucleated red corpuscles.

As has been indicated already in Section 1. I consider that the relation of the nucleated red corpuscle to the blood in Variola is not a specific one - that this cell makes its appearance at the same time, and under the same circumstances as the Myelocyte, and that its association with this and other cellular types from the marrow is accidental.

It is to be noted that the presence of pyogenic organisms in the bone-marrow is not accompanied by a corresponding proliferation of the leucoblastic elements, and that evidences of a polymorpho-nuclear reaction are absent. It would therefore, appear to be the case that there is either a loss of potentiality of such a reaction induced by the variolar poison, or, that such invasions of the marrow, as of other tissues, occur at such a late stage of the illness, that no reaction is possible.

It is probable that both these causes contribute to the result, the "passive" nature of microbic invasions in particular having been noticed both in the skin and in the spleen.

SECTION 4.

THE SPLEEN in VARIOLA.

The condition of this organ in Variola is a very variable one. The researches of Golgi and Ponfick on the subject led these authors to conclude that the Spleen presented different characters in different types of Variola. They stated that in confluent, abundantly suppurative cases, the Spleen was enlarged, soft and congested and that the Malpighian bodies were voluminous and relatively prominent.

In cases of haemorrhagic Variola on the other hand, the organ was small and either firm or soft, sometimes with wrinkled capsule.

Later observations have shown, however, that this distinction in common with the similar one which Golgi found for the bone-marrow cannot be maintained.

Various observers have since placed on record cases in which the condition of the Spleen varied considerably both in the suppurative and haemorrhagic varieties. One of the most recent of these (M.Arnaud) distinctly states that the condition of the Spleen in haemorrhagic cases of Variola has nothing specific or characteristic about it.

The results of post-morten examinations made by

M.Weil show that the Spleen in confluent suppurative cases is as frequently of normal dimensions as it is found enlarged and either firm or diffluent, its condition depending largely on the degree of passive congestion present. The examination of confluent cases complicated by haemorrhages and of primary haemorrhagic cases gives similar results, though it must be added that in the latter, a firm Spleen of small size or of normal dimensions is somewhat more frequently met with than an enlarged diffluent condition of the organ.

I have personally noted the condition of the Spleen post-mortem in 31 cases. An analysis of these gives results which are closely comparable with those of Weil. Thus, of 18 cases in which the eruption was confluent on the face and almost so over the body, the Spleen was enlarged and congested in 13, whilst in 5 its normal dimensions were maintained. In 7 primarily haemorrhagic cases, the Spleen showed some degree of enlargement in 3; in the remaining 4 it was neither enlarged nor reduced in size. In 5 confluent cases accompanied by haemorrhage, enlargement and congestion of the Spleen was present in all. One case (of comparatively mild Variola in aged subject) in which the Spleen was slightly enlarged and congested has not been

included in the foregoing analysis.

The histological study of the Spleen in Variola has been pursued mainly hitherto from the general point of view, and the reaction of the organ in relation to the changes in the blood and haematopoietic organs has only recently been made the subject of enquiry.

Golgi considered that the Spleen exhibited changes which are comparable to those which he found in the bone-marrow. Thus in haemorrhagic cases he described nucleated red corpuscles as being abundantly present, while the leucocytes were sparse and degenerated; in suppurative variola "giant cells" and leucocytes were found to be numerous while nucleated red corpuscles were exceptional.

The reaction of the Spleen, however, cannot be regarded as offering such definite distinctions in different cases.

M.Bezançon, who examined the Spleen in 6 cases of Variola draws attention to the presence of mononuclear leucocytes amongst the lymphocytes of the Spleen and speaks of collections of such cells and even of polymorphonuclear leucocytes in certain situations. He also observed the presence of endarteritis in the smaller vessels, but was unable to confirm Weigert's observation that small focal necroses occurred in the Spleen.

M.Arnaud finds that the Splenic lesions are very similar in the two more severe forms of the disease (Confluent and haemorrhagic). He describes the Malpighian bodies as being generally hypertrophied in haemorrhagic cases and also speaks of the connective tissue of the capsule, the trabeculae of the pulp and the finer fibrous stroma as being the seats of inflammatory irritation.

M.Weil has examined the Spleen histologically in 15 cases. The general observations of M.Arnaud are confirmed by this author who states in addition that the Spleen like other organs in Variola undergoes a "myelogenic transformation". Evidences of this are to be found, according to M.Weil, in the proliferation of large mononuclear cells which occurs under the capsule, round the capillaries and especially at the periphery of the Malpighian follicles.

With regard to the cellular types met with in the Spleen, Weil finds that all those which are found in the bone-marrow are reproduced here. The predominating type of cell is the mononuclear with and without neutrophile granulations. The latter which vary in size and staining reactions, preponderate.
Megacaryocytes and plasma cells are also found, the former being sometimes fairly numerous. Eosinophile cells

especially of the polymorpho-nuclear variety, are sometimes numerous but more generally are reduced in numbers. Polymorpho-nuclear neutrophiles are very exceptionally met with. Nucleated red corpuscles, which are not readily demonstrable in the Spleen in confluent cases become in haemorrhagic cases fairly abundant.

M.Weil concludes that the Spleen, under the influence of the Variolar infection assumes functions which in normal circumstances are confined to the bone-marrow and that its activity therefore in generating similar cellular forms is to be regarded as an aid to the functions of the latter tissue in combating the specific infection.

I have examined the Spleen microscopically in 7 cases, 4 of which were confluent, 1 semi-confluent, 1 confluent with haemorrhages and 1 of primary haemorrhagic character. These observations were made from both films and sections. As the results obtained offer no marked contrast in the different cases, they may be grouped in a general statement.

With regard, first of all, to the general lesions present, I have observed that the degree of congestion of the organ which occurs is a very variable one and that the microscopical appearances in consequence

differ widely. In all the cases examined, distention of the smaller veins and of the venous sinuses of the pulp has been a feature more or less marked. In some cases it has been so great as to lead to haemorrhages of local or diffuse character. The separation also of the lymphoid elements of the pulp by the distended sinuses gives the impression that these are relatively reduced, and I am unable to avoid the conclusion that in some of the cases a certain loss of lymphoid tissue actually occurs.

The Malpighian bodies have not appeared to me to be hypertrophied if by this term there is implied an increase in their lymphoid elements. If the Malpighian follicles are enlarged on naked eye examination, they are at the same time diffuse, without definite outlines. Microscopically, this appears to correspond with the fact that the capillaries traversing the follicle participate equally in the engorgement with the venous channels and capillaries of the pulp and the follicle thus occupies a greater volume than normal. The degree of engorgement is indeed sometimes such that the Malpighian follicles are scarcely recognisable in microscopical sections. Only in two cases have I observed an increase of the mononuclear hyaline cells of the Spleen

at the periphery of the follicles and, so far as my observations go, I have been unable to confirm the subcapsular or peri-arterial proliferation of these cells as described by Weil and interpreted by him as related to a myelogenic transformation of the organ. Such areas of hyaline cell proliferation appear to be comparable with those - often much more marked - which occur in Typhoid Fever, severe cases of Diphtheria and other infectious diseases. A cellular proliferation of this kind although it must be regarded as one of the evidences of the tissue reaction in infective disorders does not provide an adequate basis for the hypothesis that the Spleen in these conditions assumes a rôle compensatory to, if not interchangeable with, that of the bone-marrow in producing cell types which are normally foreign to it.

Moreover, the occurrence, and so far as I can observe, the exclusive occurrence, of cells of bone-marrow origin in the Sinuses of the Spleen goes far to show that this organ (like others) receives such cells from the blood and, from the very intimate relations between the tissue of its pulp and the capillaries, retains them in relatively greater numbers than is the cases elsewhere.

With regard to the connective tissues of the Spleen in Variola, small areas of hyaline degeneration

are not infrequent in them. These are more readily seen in the trabeculae and the walls of the smaller arteries than in the capsule. The intima of the arteries appears to be more frequently affected but the same change may be detected in the middle coats of larger vessels.

Degeneration of the endothelial cells in the vessels and occasional invasion of their coats by leucocytes are also to be noted. I have not observed actual necrosis of the trabecular or lymphoid tissues, as described by Weigert, apart from the occurrence of masses of organisms in the pulp.

The study of the cells formed in the Spleen pulp and sinuses furnishes results which reflect the character of the blood in Variola. In the vessels, lymphocytes and medium sized hyaline mononuclear cells are the most abundant; polymorpho-nuclear neutrophiles are only very exceptionally seen. Sometimes such cells are encountered amongst the lymphoid elements in advanced stages of degeneration and in somwhat rare instances they may be observed undergoing disintegration in the interior of large hyaline cells. More frequently,

however, red corpuscles are seen in the interior of such cells, which often contain in addition small granules of yellowish pigment.

Mononuclear neutrophiles are not difficult to discover in the Spleens of the severe cases examined but they are not very abundant. Eosinophile cells are found in the Spleen in very variable numbers. They are distinctly increased in certain cases (Case 12, Section2) and reduced in others; mononuclear eosinophiles are very rarely seen.

Nucleated red corpuscles are not infrequent; they have not appeared to be more numerous in one case than another. Multi-nucleated cells or cells with very large contorted nuclei (megacaryocytes) were met with pretty frequently especially in the spleen of case No.14: these cells, as well as the larger hyaline mononuclears, were filled with red corpuscles or portions of these cells.

Mitotic figures or other evidences of cellular proliferation are not a common feature of the Spleen in the cases examined.

It must be added that evidences of cellular degeneration and fragmentation are frequently observed and sometimes constitute a distinctive feature in the Spleen.

Many of the cells contain fragmented spherical nuclear masses closely resembling the forms assumed by degenerated polymorpho-nuclear cells, and there is little doubt that many of the effete cells of this class are destroyed in the Spleen.

The occurrence must also be mentioned of minute bodies staining very intensely with nuclear dyes, and similar in all their characters to those met with in the Skin.

As mentioned earlier, small masses of micro-organisms are by no means infrequent. They appear to consist either of pyogenic cocci or possibly of pneumococci in some instances. Beyond a limited area of necrosis, such collections of organisms are not connected with any tissue reaction, and it is surmised that their invasion of the Spleen occurs shortly before death.

The Spleen in Variola appears to play a more or less passive rôle; it is mainly concerned with the digestion and destruction of leucocytes which have suffered degenerative changes in the blood stream.

I cannot agree with Weil in according it a temporary myeloid activity as an aid in the struggle against Variols. Although it contains many cells peculiar to the latter tissue, they do not appear in themselves

possessed of any proliferative activity, and are more probably in every case emigrants from the bone-marrow to the blood.

The depleted condition of the Spleen pulp, as far as its lymphoid elements are concerned however, would lead one to consider that if it possesses an active phase of function this may be in the direction of giving up such cells to the blood and thus serving as an adjuvant to the similar part played by the lymph-glands throughout the body.

Its function therefore in relation to the blood appears closely similar to that of the lymphatic glands, though the lymphocyte-production of the latter is more marked. In dealing with degenerated and functionally inert cells the Spleen appears to exercise on the blood the same functions as are performed by the lymph-glands for the skin during the eruptive period.

THE LYMPHATIC GLANDS in VARIOLA.

SECTION 5.

Enlargement of the superficial groups of lymphatic glands during Variola is a readily observed clinical fact of very frequent, but not absolutely constant occurrence. In the mildest forms of the disease, glandular enlargement, very slight in degree, is either confined to particular groups of glands (e.g. the sternomastoid chain, in cases where the eruptive elements over the face and neck considerably exceed in number those occurring over a similar area of any part of the trunk or limbs) or is absent altogether.

In the more severe cases however, and especially in those characterised by an abundant eruption of semi confluent or confluent character, the glandular enlargement is a feature of practically constant occurrence.

The most severe cases of Variola, accompanied by either diffuse subcutaneous haemorrhages or by haemorrhage into the vesicles, do not show enlargement of the lymphatic glands to any degree, and it is only an occasional feature of these cases.

A slight degree of glandular enlargement may be noted at an early stage of the disease, some of the inguinal glands being appreciable when the prevariolar

or prodromal eruption is most marked over the lower part of the abdomen and inner aspects of the thighs. From this period till the acme of the true eruption has been reached, the enlargement is progressive but never extreme; with the dessication of the eruption the glands more or less rapidly regain their normal dimensions.

The glandular enlargements, even when most pronounced, are, as a general rule, painless, a sense of tension or discomfort in the axillary or inguinal regions being at most complained of. I have never observed the occurrence of suppuration of glands which have undergone enlargement during Variola, and conclude that this must be a phenomenon of the rarest occurrence. M.Lelandais attributes a certain favourable prognostic value to the presence of glandular enlargement in Variola, and this is doubtless true. But other and more certain means of prognosis are always available, and I believe that the condition of the superficial glands is to be regarded mainly as affording evidence of the presence or absence of a reaction consequent on the condition of the skin. Generally speaking, the enlargement of the glands is directly proportional to the amount of the eruption and to the degree of cell-destruction which is taking place in all its elements. The nature of the processes occurring

in the skin in Variola naturally leads one to infer the presence in the glands related to it of interesting changes of a corresponding nature.

Weil gives the results of his examination of the glands in 12 cases. His observations may be thus summarised:-

The cortical lymph sinuses and cavernous sinuses of the medullary portion are distended with cells of various types. Most frequently, lymphocytes ("globulins") and large mononuclears with clear nucleus abound. In the central sinuses and round the follicles however, according to Weil, all the forms met with in foetal bone are seen. Of the cells possessing granules, the mononuclear neutrophile is the most abundant. Polymorpho-nuclear, eosinophile and basophile cells are almost always present. Megacaryocytes of medium dimensions are sometimes encountered. Nucleated red corpuscles are found only in the infant or in haemorrhagic cases. Polymorpho-nuclear neutrophiles are only very exceptionally met with. The presence of cellular degeneration is also noted, as well as occasional sub-capsular haemorrhages and micro-organisms. The latter are spoken of as existing either in the sinuses or vascular capillaries, causing thrombosis in the latter situation. This author has also recorded

the results of his examination of the periglandular Connective tissue. This, which in certain cases had undergone some proliferation, was found to contain many hyaline cells both of the small and the large varieties. Cells possessing granules, however, were but infrequently found in this situation. The cellular infiltration of this tissue causes M.Weil to make the suggestion that the connective tissue generally throughout the body, and the periglandular connective tissue in particular may in circumstances similar to that under consideration, assume a leucocytopoietic function.

In concluding, Weil states that the lymphatic glands, like the Spleen, undergo in Variola a myeloid transformation, in many respects comparable to that which occurs in Myelogenic Leukaemia.

In appending the results of my own observations, I cannot but regret that these were made towards the close of my work, and are necessarily limited in number. They are based on microscopical sections and cover-glass films prepared from the cellular juice of the gland pulp. Both sections and films were stained after appropriate fixation in Ehrlich's triacid fluid, Carbol-thionin blue with or without eosine, and Haemalum and Eosine.

Obs.1.L. aged , died 16th day of disease. Confluent

on face, semi-confluent on trunk and limbs. Left inguinal gland examined. The gland is enlarged, and presents marked capillary congestion. Endothelial cells of cortical sinus are swollen, granular and largely desquamated. The contents of the sinus are:-

Lymphocytes most abundant.

Red Corpuscles fairly numerous.

Large Hyaline Cells fairly numerous.

Polymorpho-nuclear eosinophiles occasionally seen.

Polymorpho-nuclear neutrophiles absent.

Both mono- and polynuclear eosinophiles are observed in the periphery of the cortical follicles. Here also a few degenerated polynuclear neutrophiles are observed. Cellular fragments and minute spherical masses of free nuclear matter are also seen both in the cortical follicles and medullary lymphoid reticulum . Large phagocytes occur occasionally, sometimes enclosing cellular fragments. The"germ centres" of the follicles are almost entirely obscured by the density of the lymphoid cell aggregations.

Obs.2. Gland. Haemorrhagic Smallpox.

Lymphocytes and larger hyaline cells are present in very considerable numbers in the cortical sinus. Other cell types met with here are eosinophiles (both mono- and polynuclear), nucleated red corpuscles, and numerous

degenerated endothelial cells. No appearances of polymorpho-nuclear neutrophiles are discovered in the sinuses lymphoid tissue or capillary blood vessels. No organisms are seen.

Obs.3. Male, aet 31. Haemorrhagic Smallpox. Death after 6½ days illness. Film from gland stained with Ehrlich's fluid.

A good many eosinophile cells of both classes seen. Red blood corpuscles numerous. Some of these are apparently undergoing intra-cellular disintegration. No nucleated red corpuscles observed. Spherical masses of free nuclear matter are not uncommon. No polymorpho-nuclear neutrophiles seen.

Obs.4. Child, aged 13. (Film preparations).

Red corpuscles seen in considerable numbers. Examples of phagocytosis fairly frequent (cells of lymphocyte type and red corpuscles both undergoing digestion). Eosinophile cells with both types of nucleus are pretty common. Polymorpho-nuclear neutrophiles are not seen. No organisms discovered.

Obs.5. Eliz. Mc C. aet 4. Unvaccinated. Died 10th day of disease.

Cortical sinus occupied by numerous lymphocytes and larger hyaline mononuclear cells. Red corpuscles fairly

numerous in sinus, some undergoing intra-cellular digestion. Eosinophiles met with chiefly in central sinuses of gland. A few polymorpho-nuclear neutrophiles, for the most part showing only slight signs of degeneration, are discovered in the sinuses. No free nuclear masses encountered. The germ-centres of the follicles are obscured by lymphoid cell multiplication.

The above observations, although furnishing an altogether inadequate basis for a complete statement as to the role of the lymphatic system in the Variolar infection, provide unmistakeable indication of the marked functional activity of theglands during the eruptive period.

This activity is manifested in two directions: (1) The activity of the lymphoid tissue is doubtless related to the special variety of leucocytosis induced in Variola viz. a leucocytosis characterised by preponderance of the hyaline type of cell, especially of the lymphocyte. (2) The contents of the lymph-sinuses indicate the extent to which the cellular lesions occurring in the skin are borne by the glands. A certain correlation can I believe be established between the contents of the cortical sinus and those of the elements of the eruption. Thus in cases characterised by an abundant and fully developed eruption, the cells met with in the sinuses

comprise both varieties of hyaline cell, with eosinophile and, exceptionally, polymorpho-nuclear neutrophiles or their remains. Fragments of cells and free nuclear masses are also found conveyed thither.

M.Labbé has observed the presence of occasional free nuclear masses in the germ-centres of the follicles of healthy glands, but the presence of cellular and nuclear debris in the cortical sinus leaves no doubt as to the mode by which the results of the process in the skin are dealt with. The appearance in haemorrhagic cases, in addition to the elements noted, of red corpuscles in fairly large numbers, including examples of the nucleated variety, and of cells enclosing red corpuscles or their remains sufficiently indicates the related activity of the glands to the cutaneous haemorrhages.

It will be noted that my observations have been made on the glands in semi-confluent and haemorrhagic cases - in the very cases in which, from our knowledge of the condition of the blood as regards myelocytes and the occurrence (rarely, it is true,) of these elements in the cellular contents of the eruption, one moght have expected, a priori, to meet with them also in the lymphatic glands. This is not borne out by my observations, and I have been quite unable to confirm the statement made

by Weil that the mononuclear neutrophile cell is constantly present in the lymphatic glands. I am also unable to agree with him in the view that the glands undergo a "myeloid transformation". To attribute a specialised function of this kind to lymphatic tissue either in Variola (or Myelogenic leukaemia, with which Variola is compared by him) appears to be alike unnecessary and unsupported by facts.

I am led to the belief that the increased functional activity of the lymphatic system is directly related, on the one hand, to the positive chemiotaxis displayed particularly towards the smaller hyaline cells and lymphocytes, including the characteristic lymphocytosis of Variola, and on the other, to the fact that the glands bear the brunt of the cell-degenerations and necroses so extensively present during the eruptive period.

THE LIVER and KIDNEY in VARIOLA.

That the parenchymatous tissues of these organs suffers very profound changes during Variola is a sufficiently well known fact.

The Liver as seen post-mortem is enlarged and its lobular markings are obscured by the existence of a marked degree of cloudy swelling. The presence also of fatty changes which overtake the cells of the entire lobule (as seen in the low power photograph in Fig.24.) is a feature of such constant occurrence in Variola that it may be regarded as a part of its morbid anatomy.

The more sensitive epithelium of the Kidney suffers similar changes. These may consist in cloudy swelling with a varying degree of desquamation of the lining cells of the tubules and the formation of occasional hyaline casts. In haemorrhagic cases, however, and more particularly in infants born with signs of the disease or who, having never been vaccinated, have succumbed to Variola in a severe form, I have observed glomerular and tubular changes in the Kidney which must be assigned to an acute nephritis. As a somewhat analogous fact may be mentioned the occasional occurrence of nephritis following vaccination where the local or general symptoms have been severe.

I am not so much concerned at present however with changes of the Kind mentioned above as with the occurrence of certain cellular areas of infiltration which appear in the **interstitial** tissues of both organs in Variola.

In the Liver, many of the portal areas are the seat of a leucocyte infiltration of sometimes marked character. Between the fibrillae of the connective tissue in this region are numerous cells which, aggregated most closely round the portal veins may be seen extending on all sides in the margins of the neighbouring lobules, (See Fig. 25.) whose cells have a granular degenerated appearance.

In the Kidney also such cellular collections may be seen mapping out the planes of interstitial tissue between the tubules both of the cortex and pyramid. They are usually most pronounced either immediately under the renal capsule or round the straight vessels near the apex of the pyramid. (See Fig. 26.) In general, one is reminded of the very similar appearances presented in the acute interstitial nephritis of Scarlatina.

It is probable that in both organs such areas of infiltration with local connective tissue activity may be the starting points of a post-infective cirrhosis.

If one studies the cellular types which comprise these areas of interstitial infiltration, one finds that both in the Liver and Kidney, the lymphocyte and smaller hyaline cell is the most abundant. Hyaline cells of larger size are present in much smaller numbers, and some elements are apparently derived by division of connective tissue corpuscles. I have seldom seen eosinophile cells in such areas and polymorpho-nuclear cells are of rare occurrence. M.Weil states that the mononuclear neutrophile may be found in these situations in the liver which he designates "nodules infectieux", and raises the question whether the liver may not acquire during infectious diseases something of a haematopoietic activity. I have not been able to determine the presence of Myelocytes of neutrophile or other variety though, from the condition of the blood, their occasional occurrence might be looked for.

The cells met with in the interstitial tissues of the Kidney have similar characters. It should be added that the vast majority of the nucleated cells present in any vessel included in the section have the characters of lymphocytes, polymorpho-nuclear cells being but rarely encountered.

Such a condition, which really amounts to a

tissue lymphocytosis is of considerable interest when the nature of the changes in the blood are called to mind. What its full significance may be it is as yet impossible to say; it may be connected with the presence of the parasite of Variola which seems to attract cells of a similar type to the Skin. It serves to indicate at least that the character of a leucocyte emigration in infective conditions is determined by the nature of the leucocytosis induced by the disease in the blood.

It may be reasonably inferred that the pursuit of similar cellular studies in other infectious diseases would yield equally interesting results.

G E N E R A L C O N C L U S I O N S.

The principal conclusions which are to be drawn from my work I now submit as follows:-

(1) That Variola in all its forms is accompanied by leucocytosis. This is most marked in cases characterised by abundant eruption. The leucocytosis precedes the eruption in all cases except the very mildest, attains a maximum when the cutaneous reaction is at its height (8th or 9th day of the disease) and subsequently slowly declines. The leucocytosis present in haemorrhagic cases is moderate in degree and transient in character.

(2) The leucocytosis offers a marked contrast to that present in other infectious diseases in respect that it is characterised by the relative and absolute increase of lymphocytes and medium sized hyaline cells. This is accompanied by a relative reduction of polymorpho-nuclear elements. From the point of view of absolute numbers, however, these are usually increased.

(3) Varying directly with the degree of severity of the case, the character of the leucocytosis is modified by the appearance in the blood, of cellular elements from the bone-marrow.

(4) The condition of the haematopoietic organs - more particularly of thebone-marrow and lymph-glands is one

of proliferative activity, and directly related to the leucocytosis. This increased functional activity, often visible post-mortem in the lymph-glands, is not usually so evident in the bone-marrow, which post-mortem more frequently exhibits appearances due to a varying degree of depletion of its leucoblastic elements.

(5) The leucocytosis of Variola is reproduced in its characteristic features in the cutaneous eruption. The presence of pyogenic organisms in the eruption is an accidental occurrence which in the comparatively small number of elements so invaded does not materially affect the character of the leucocyte emigration.

(6) Both in the blood and in the skin the leucocytosis must be regarded as a means of defence against the specific cause of the disease.

B I B L I O G R A P H Y.

The Blood and Haematopoietic Organs.

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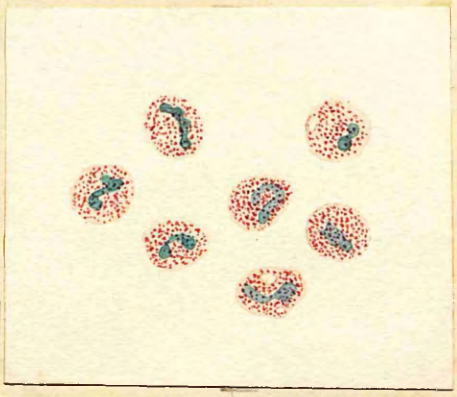
FIGURE 1.



The cells figured were drawn from the blood of Case No14. They illustrate the comparatively simple nuclear forms of many of the neutrophile cells from the 10th day of disease onwards. Although the cells in the figure were sketched from the blood of a severe case, such forms occur in all cases of Variola of moderate severity, and were absent only in the very mildest cases. The presence of occasional vacuoles will be noted.

FIGURE 2.

(a) Vacuolated polymorpho-nuclear leucocyte. Nucleus feebly stained.

(b) Healthy polymorpho-nuclear leucocyte in immediate vicinity, with characteristic staining.

(c) Degenerated polymorpho-nuclear leucocyte. Nucleus very faintly stained. Neutrophile granules diminished.

(d.e.) Lymphocytes showing variations in depth of nucleus staining and tint of protoplasm. "e" is not unlike a nucleated red corpuscle. (Sketched from Case No.11.)

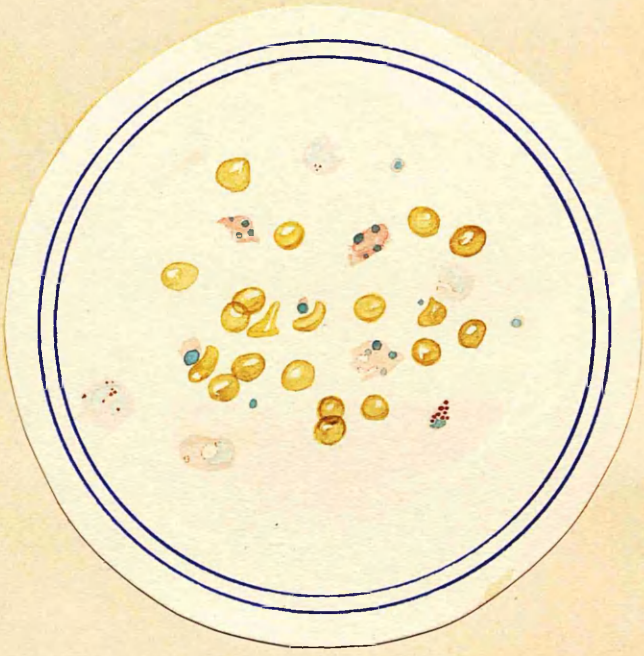
Such features in the cell types represented are frequently met with in moderately severe cases of Variola such as this.

FIGURE 3.

The sketch represents different types of nucleated red corpuscles encountered in a case of moderately severe Smallpox. These cells which came under observation during theleucocyte count were sketched as they occurred, and placed together in an imaginary microscopic field. Attention is drawn to thevariety of forms which the nucleus has assumed in these cells.

Film fixed by heat. Ehrlich's triacid fluid.

FIGURE 4.



Blood from severe case complicated with haemorrhages. The sketch represents the extreme forms of leucocyte degeneration encountered in several microscopic fields. The polymorpho-nuclear cells show fragmentation of nucleus loss of neutrophile granules, and the occurrence of vacuoles. A fragment of an eosinophile cell is represented in the lower right hand portion of sketch. Free nuclear masses or bodies composed of a minute spherical nucleus with delicate envelope of protoplasm were also frequently encountered in this case.

Film fixed by heat. Ehrlich's triacid fluid.

FIG. 5.

FIGURE 5.

High power drawing of the appearances presented at an early papular stage of the Variolar eruption. The epithelium is increased in its vertical diameter. This is due partly to the existence of a localised oedematous condition in the cells of the mesial prickle layer and partly to swelling and vacuolation of the cells of the Malpighian layer. In the former situation an area will be observed in which the cells are slightly swollen with indefinite borders and with impaired nuclear staining. In some of these also a considerable enlargement of the peri-nuclear space has occurred. It is in this zone that the earliest sign of vesicle-formation takes place. Peri-nuclear vacuolation is noticeable to a marked degree in a few of the cells of the Malpighian layer. Immediately beneath this layer a series of minute irregular spaces are noted. These represent lymphatic spaces distended with fluid. In some of these at the apex of the papilla represented in the centre are a few minute definitely rounded bodies of variable size staining rather faintly with the nuclear dye. These, which agree with the description of Pfeiffer's parasite in Vaccinia and Variola are scarcely to be explained as degeneration products of altered cell-plasm or fragmented nuclei at such an early stage of the eruptive phenomena.

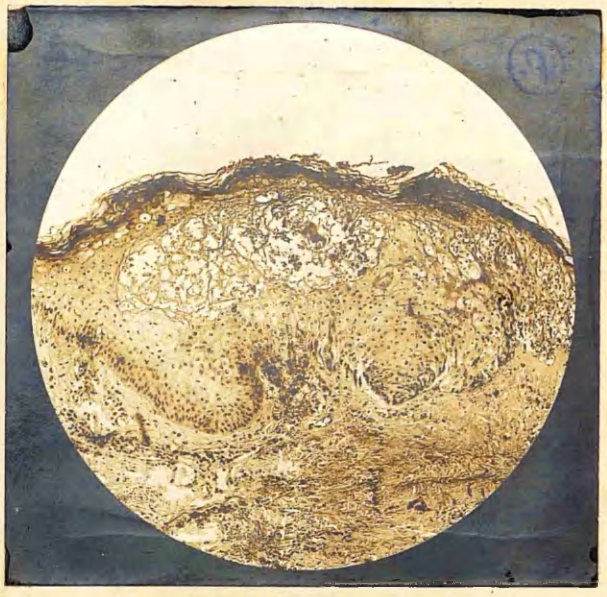


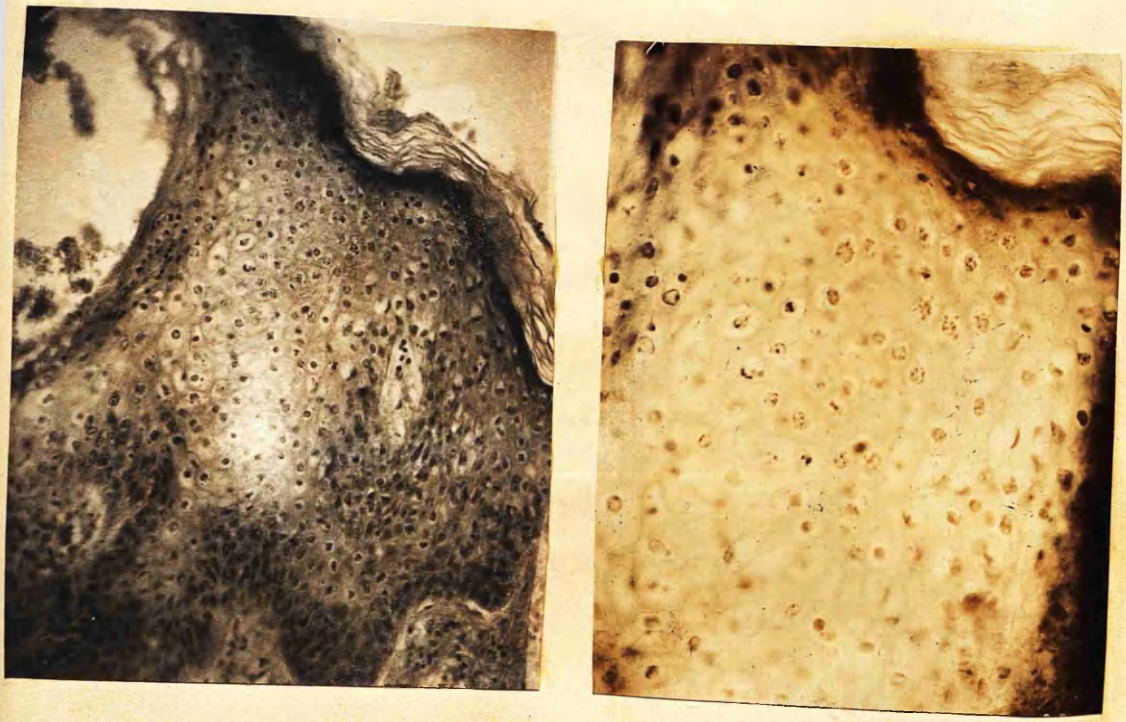
FIGURE 6.

The photograph illustrates the histology of a comparatively early Variolar vesicle. The vesicle is situated in the mesial prickle zone, and is formed as described elsewhere, by the coalescence of cells which have undergone reticular colliquation. The septa formed by the persistent mantles of such cells are clearly visible as delicate lines sometimes preserving the outline of swollen cells.

The condition of the Malpighian layer beneath the vesicle is well shown. Some of its cells are swollen, while others are seen to be considerably narrowed and elongated. The almost complete absence of leucocyte infiltration in the hypoderm will also be noted.

65 Diam.

FIGURE 7.



Microphotographs showing nature of epithelial changes at the margin of Variolar vesicle.

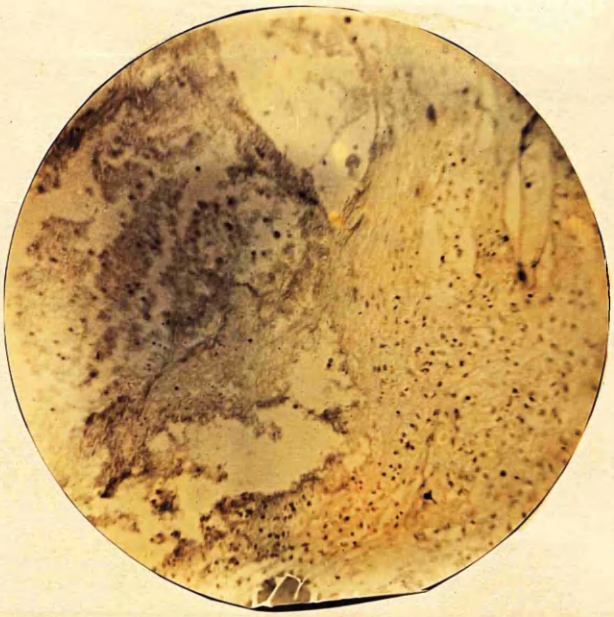
In that under medium power (to the left) the proliferating cells of the Malpighian layer are seen, and also the clear vesicular condition of the cells in the prickle zone. The presence of a small secondary vesicle in this zone may also be noted. The amount of leucocyte infiltration at the periphery of the vesicle is slight.

The photograph to the right (under high power lens) represents the mesial prickle zone in the same

field as that from which the other photograph is taken. The vesicular condition of the cells with their crescentic or fragmented and granular nuclei is well seen.

Here and there the presence of minute "bodies" in the peri-nuclear vacuole can be made out.

FIGURE 8.



Margin of Variolar "pustule" illustrating the very moderate leucocyte infiltration which occurs at the periphery of the Element and also the somewhat sparsely cellular character of the contents in some cases.

In the cavity of the smaller vesicle to the right a multi-nucleated cell with peripherally arranged nuclei is visible. Such cells occur very rarely in the Variolar eruption, though they appear to be more common in Varicella.

FIGURE 9.

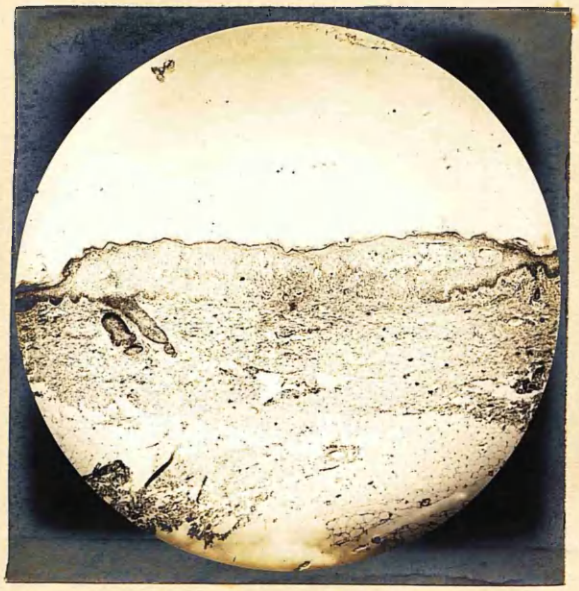
General low-power microphotograph of Variolar pustule, 9th day.

The deeper layers of the epithelium are observed to be considerably broken up beneath the pustule, which, in this instance, is a comparatively simple cavity. It is noteworthy that although the element represented contained Streptococci (See Figs. I8.) the cellular element present is comparatively scanty.

FIGURE 10.

Photograph (35 diam.) showing general relations of the pustule to the skin at the 9th day. The comparatively simple nature of the cavity, which is traversed completely by only two or three strands of epithelial cells, is well seen. Indications of the finer septa may also be obtained. The epithelium of the Malpighian layer, which is almost completely destroyed below the centre of the pustule, is in a state of activity at the margins where it appears darker in the photograph.

FIGURE 11.



Photograph (17 diam.) showing two pustules which have coalesced in a semi-confluent case, accompanied by haemorrhages. The Malpighian layer beneath the centre of the conjoined elements is completely destroyed. This situation (represented as darker in the photograph) is the seat of a subcutaneous haemorrhage with infiltration of the surrounding tissues with blood corpuscles. The complete destruction of the superficial parts of a hair follicle (as seen on the left) is not observed except in severe cases.

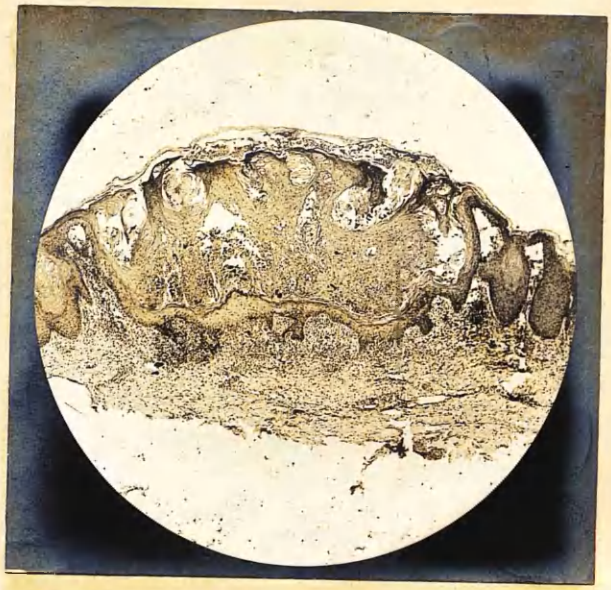


FIGURE 12.

The photograph illustrates the appearances seen in a vesicle in which healing has commenced. The formation of a thin corneous zone at the base of the vesicle is observed (indicated in the photograph by a thin dark line surmounting the cushion of epithelium beneath the vesicle).

In the particular section (which is one of a series) from which the photograph is taken, the epithelial laminae traversing the vesicle are of considerable volume.

Surmounting the old corneous layer over the summit of the vesicle, the remains of the "scab" or crust are apparent.

25 diam.

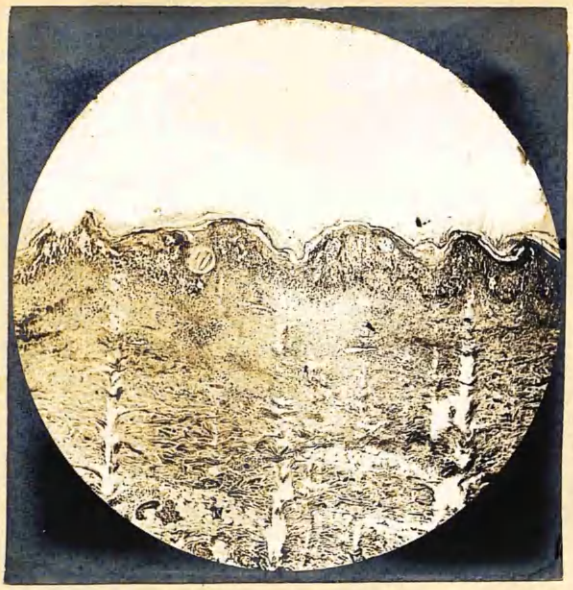


FIGURE 13.

Photograph (35 diam.) showing the more or less continuous destruction of the skin which occurs in a confluent case of Variola. The mesial prickle layer is transformed into a series of irregular vesicles which generally extend throughout the entire thickness of the skin. The continuity of the Malpighian layer is very much interrupted and there are areas of leucocyte infiltration and necrosis extending for a considerable distance into the hypoderm.

FIG. 14.

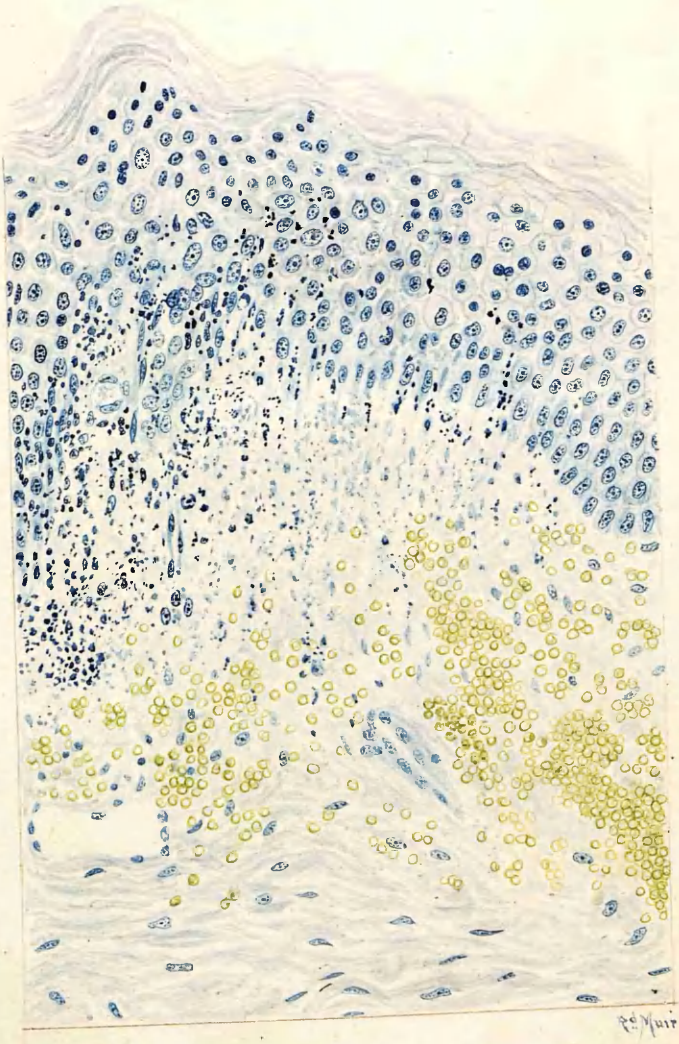


FIGURE 14.

High power drawing of skin and subcutaneous tissue from a case of true haemorrahgic Smallpox. The haemorrhage has occurred beneath the skin which is free from eruptive manifestations. A general oedematous swelling however of the cells of the mesial prickle zone will be noted. The striking feature is the presence of large numbers of deeply stained bodies of great variation in size and of irregularity in form which are apparently insinuating their way between the epithelial cells. While many of the larger are doubtless derived from nuclear fragmentation of leucocytes~~is~~ associated with the haemorrhage, the more minute are indistinguishable from the "bodies" represented in the lymph-spaces beneath the early developing vesicle in Fig5.

It will be at once apparent that such bodies are not to any extent derived from the epithelium because (1) they are primarily sub-epithelial in position and (2) the epithelium is practically free from destructive changes. Nor do I think they are entirely explicable as leucocyte dêbris. More than this my observations do not permit me to say. The suggestion may be expressed however, that in such collections a protozoan parasite may yet be found. It is these situations in haemorrhagic cases that I incline to think offer the best prospects for its cultivation.

FIG. 15.

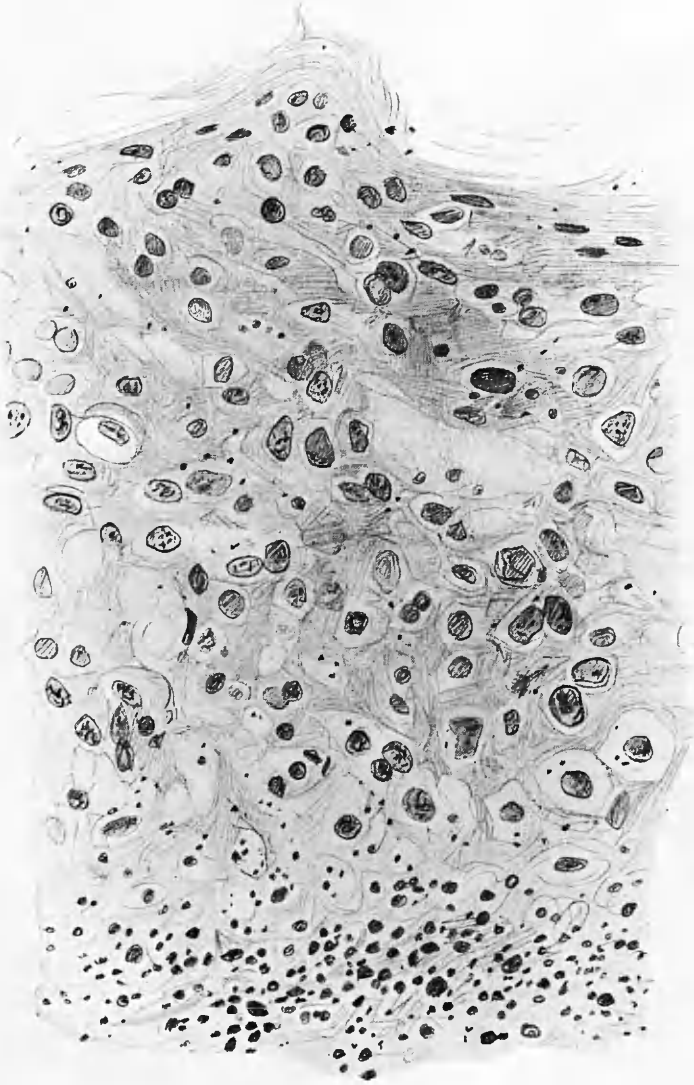


FIGURE 15.

The features represented in this figure are similar to those of the preceding. They are reproduced from a section of the skin of the forearm (Case No.16 Section 1) A general oedematous condition of the skin, more marked in the Malpighian layer will be noted. There are also several small vesicles of irregular form in the mesial prickle zone. Large numbers of minute deeply stained bodies are observed beneath the Malpighian layer - in this case not so obviously asociated with a haemorrhage into the hypoderm. Many of these may be observed inside the swollen cells, as represented more clearly in the following figure. Others however are inter-cellular, and these appear to gradually make their way to the surface of the skin.

FIGURE 16.

The sketch represents the swollen zone of epithelial cells at the margin of an extending Smallpox vesicle. Some of the cells are "ballooned" out by a large vesicle. Many show rounded or oval bodies aggregated round the nucleus and stained very deeply. These are sometimes intra-cellular in position, but more rarely. It is surmised that these are not entirely cellular or nuclear products, but that some represent the parasitic amoeboid bodies described by Pfeiffer and others.

The somewhat abrupt transition to the narrow eleidin layer is represented.

Section stained in Carbol-thionin blue. Camera lucida drawing. Zeiss 1/12" homog. immers: with Compens. Ocular. About 1000 diam.

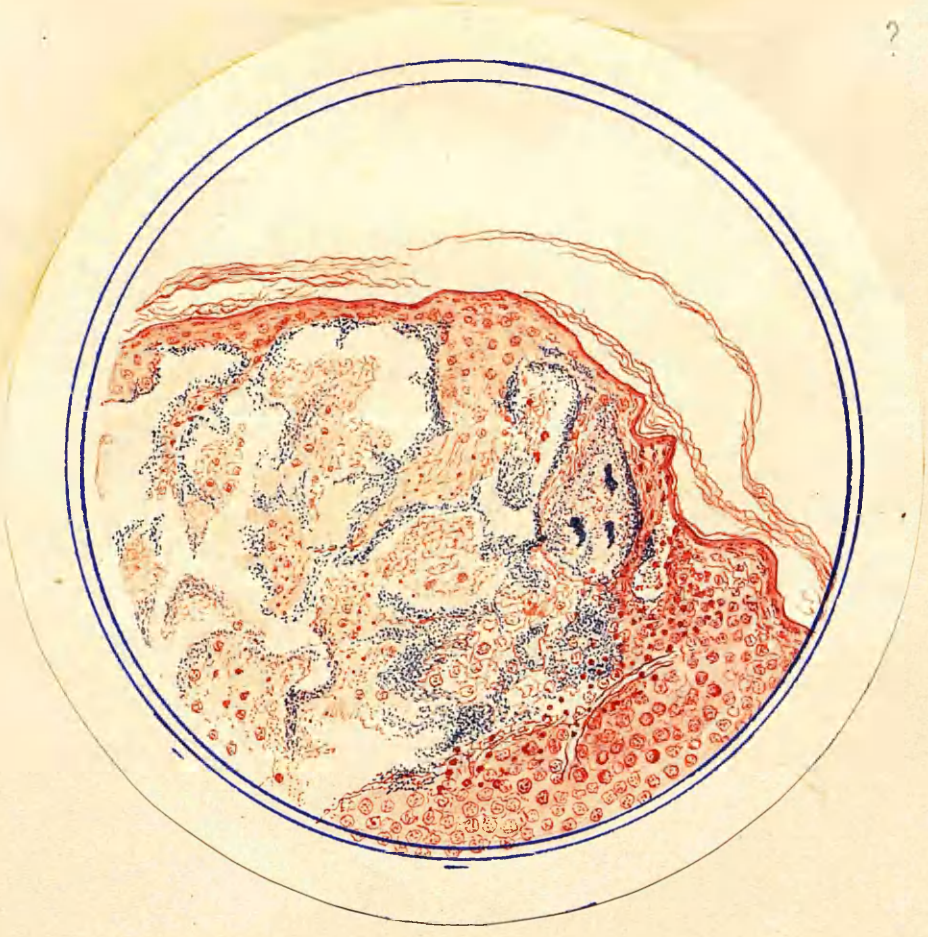
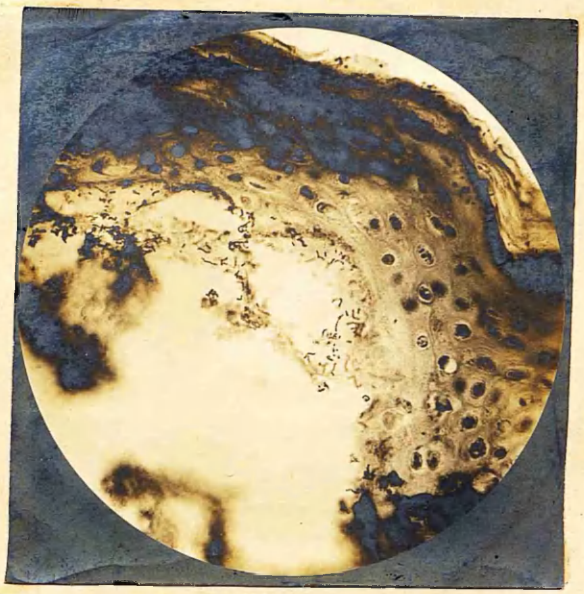


FIGURE 17.

Smallpox pustule (Infant) 10th day. Section shows invasion of pustule by Staphylococcus Pyogenes Aureus. The organism is applied to the surfaces of epithelial laminae etc, and appears to be multiplying along these. Note the insignificant leucocyte infiltration present - chiefly visible on right hand side of drawing.

Camera Lucida Drawing. Zeiss' objective BB. Eyepiece No.3. 170 diam.

FIGURE 18.



Microphotograph showing the presence of Streptococci in Variolar pustule. They are abundant in the marginal parts of the pustule on the right side.

Photograph of Streptococci in pustule (from same preparation as the preceding.) x 1000 Diam.

FIGURE 19.

High power microphotograph from the middle of the base of a series of small vesicles in a confluent case with sub-epithelial haemorrhages. In the upper part of the photograph the lower margin of the Malpighian layer can be seen - though somewhat indefinitely.

A large number of minute deeply stained "bodies" can be seen apparently making their way towards and into the Malpighian layer. Between these the outlines of red corpuscles may be discerned.

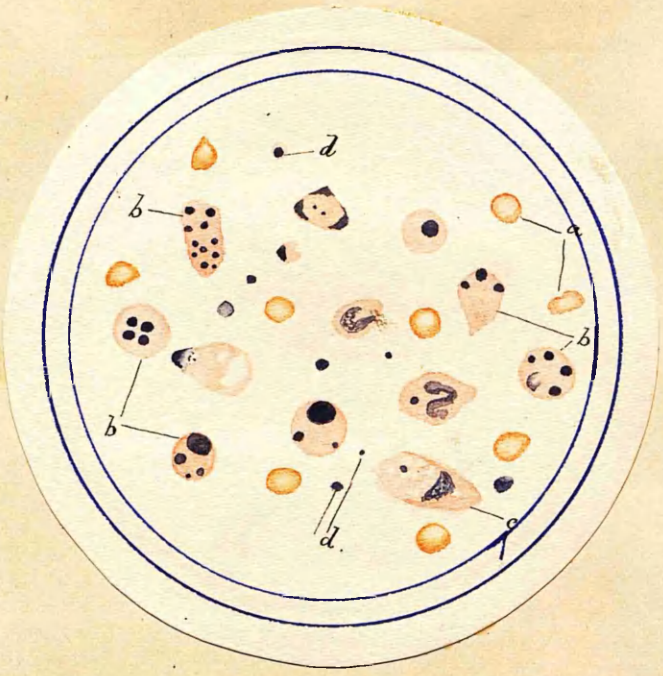


FIGURE 80.

Drawing from film preparation representing contents of early pustule. Case No.8. 7th day of illness. The forms represented include (a) red corpuscles, (b) degenerated polymorpho-nuclear leucocytes, (c) altered epithelial cells and (d) free nuclear masses of minute size, with or without a surrounding envelope of protoplasm. Haemalum. Eosine.

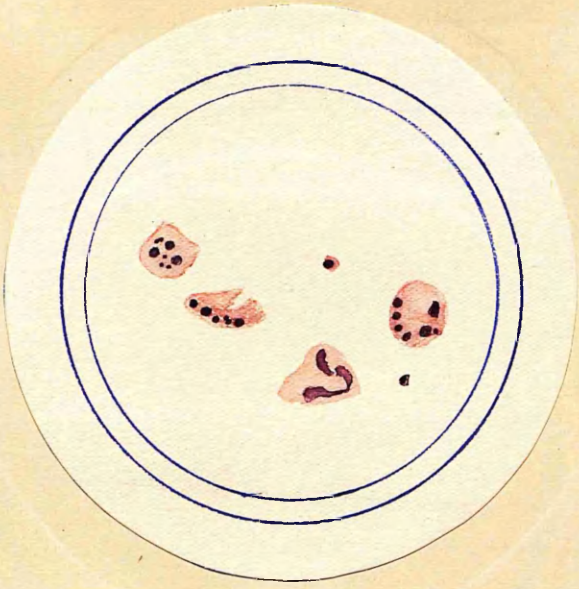


FIGURE 21.

Appearances presented by degenerated polymorpho-nuclear leucocytes in film preparation from Vesicle.

Severe case, 8th day of disease. Fixed wet in $HgCl_2$.

Haemalum and Eosine.

FIGURE 22.

Drawing from film-preparation from contents of Vesicle. Case No.8. 11th day. Carbol-Thionin blue.

Numerous degenerated polymorpho-nuclear leucocytes are represented, as well as occasional red corpuscles (faint greenish yellow in colour). Several small mononuclear cells are also to be noted, as well as altered epithelial cells.

FIGURE 23.

The drawing represents the contents of a Varicellar vesicle as seen in film-preparation, and is introduced so that its components may be compared with those of a Variolar vesicle. The close similarity of the two will be noted at once. As in the latter the cells represented are:-

Degenerated polymorpho-nuclear leucocytes. Red blood corpuscles. Hyaline cells of both classes. Altered epithelial cells. In addition intra-cellular inclusion of both red corpuscles and polymorpho-nuclear cells was observed and is represented.

FIGURE 24.

Photograph (35 diam.) of section of liver from a case of haemorrhagic Smallpox. The general fatty metamorphosis of the tissue is a striking feature. The presence of cellular infiltration of the connective tissue in the portal areas may also be detected.

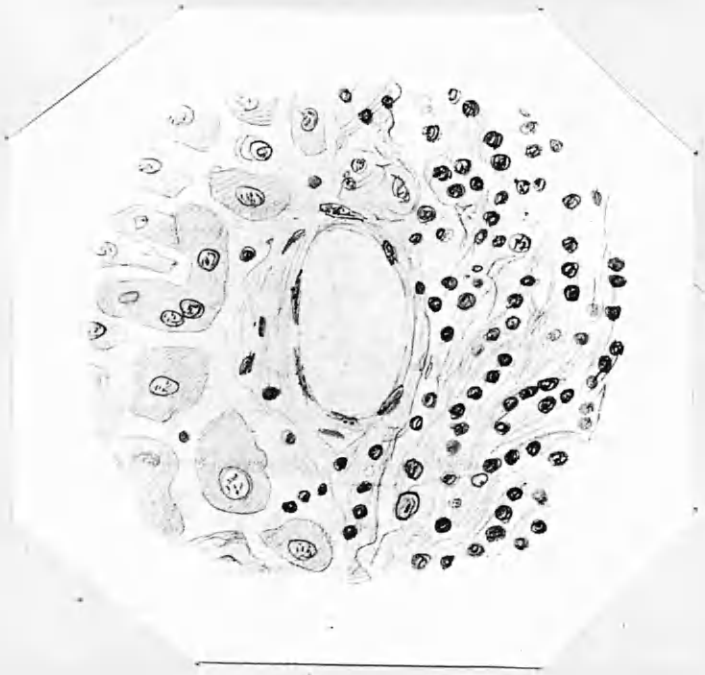


FIGURE 25.

Drawing of hepatic portal area, showing infiltration of lymphocytes between the connective tissue fibrillae of the portal tract. Amongst these cells are one or two nuclei of larger size - apparently those of degenerated liver cells. About 400 diam.

FIGURE 26.

Photograph (120 diam.) of section of Kidney from case of severe Variola. The field represented includes two of the straight vessels (dilated veins) of the pyramid, surrounded by dense leucocyte infiltration. The tubules on the right side of the field have suffered considerable compression, while the Epithelium of those on the left is granular in appearance and indefinite in outline.